RHODANINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

[0001] This application claims priority to provisional application MBHB Attorney Docket No. MBHB-03-004-A, filed October 28, 2003, and provisional application USSN 60/426,280, filed November 13, 2002.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] This invention is in the field of ubiquitin ligation and inhibitors of the ubiquitination pathway. Additionally, this invention is in the field of treating diseases or conditions associated with ubiquitination.

Summary of the Related Art

[0003] Ubiquitin is a 76 amino acid protein present throughout the eukaryotic kingdom. It is a highly conserved protein and is essentially the identical protein in diverse organisms ranging from humans to yeasts to fruit flies. In eukaryotes, ubiquitin is the key component of the ATP-dependent pathway for protein degradation. Proteins slated for degradation are covalently linked to ubiquitin via an ATP-dependent process catalyzed by three separate enzymes.

[0004] The ubiquitination of these target proteins is known to be mediated by the enzymatic activity of three ubiquitin agents. Ubiquitin is first activated in an ATP-dependent manner by a ubiquitin activating agent, for example, an E1. The C-terminus of a ubiquitin forms a high energy thioester bond with the ubiquitin activating agent. The ubiquitin is then transferred to a ubiquitin conjugating agent, for example, an E2 (also called ubiquitin moiety carrier protein), also linked to this second ubiquitin agent via a thiolester bond. The ubiquitin is finally linked to its target protein (e.g. substrate) to form a terminal isopeptide bond under the guidance of a ubiquitin ligating agent, for example, an E3. In this process, monomers or oligomers of ubiquitin are attached to the target protein. On the target protein, each ubiquitin is covalently ligated to the next ubiquitin through the activity of a ubiquitin ligating agent to form polymers of ubiquitin.

[0005] The enzymatic components of the ubiquitination pathway have received considerable attention (for a review, see Weissman, *Nature Reviews* 2:169-178 (2001); *see also* Wong *et al.*, *Drug Discov. Today* **8**(16), 46-54 (2003)). The members of the E1 ubiquitin activating agents and E2 ubiquitin conjugating agents are structurally related and well characterized enzymes. There are numerous species of E2 ubiquitin conjugating agents, some of which act in preferred pairs with specific E3 ubiquitin ligating agents to confer specificity for different target proteins. While the

nomenclature for the E2 ubiquitin conjugating agents is not standardized across species, investigators in the field have addressed this issue and the skilled artisan can readily identify various E2 ubiquitin conjugating agents, as well as species homologues (*See* Haas and Siepmann, *FASEB J.* 11:1257-1268 (1997)).

[0006] Furthermore, ubiquitin agents, such as the ubiquitin activating agents, ubiquitin conjugating agents, and ubiquitin ligating agents, are key determinants of the ubiquitin-mediated proteolytic pathway that results in the degradation of targeted proteins and regulation of cellular processes. Consequently, agents that modulate the activity of such ubiquitin agents may be used to up-regulate or down-regulate specific molecules involved in cellular signal transduction. Disease processes can be treated by such up- or down regulation of signal transducers to enhance or dampen specific cellular responses. This principle has been used in the design of a number of therapeutics, including phosphodiesterase inhibitors for airway disease and vascular insufficiency, kinase inhibitors for malignant transformation and proteasome inhibitors for inflammatory conditions such as arthritis.

[0007] There is a need for inhibitors of ubiquitination that can alter the ATP-dependent ubiquitination of proteins. Inhibition of ubiquitination can regulate the degradation of proteins in ways that assist in treating various disorders. Inhibitors of ubiquitin ligases may also help in treating infectious diseases such as bacterial and viral infections that depend on the cellular biochemical machinery.

[0008] Due to the importance of ubiquitin-mediated proteolysis in cellular process, for example cell cycle regulation, there is also a need for a fast and simple means for identifying the physiological role of ubiquitin agents that are catalytic components of this enzymatic pathway, and for identifying which ubiquitin agents are involved in various regulatory pathways. Pray *et al., Drug Resist. Update* **2(2)**, 249-258 (2002). Thus, an object of the present invention is to provide compounds, compositions and methods of assaying for the physiological role of ubiquitin agents, and for providing methods for determining which ubiquitin agents are involved together in a variety of different physiological pathways.

BRIEF DESCRIPTION OF THE INVENTION

[0009] The invention comprises compounds, pharmaceutical compositions of the compounds for inhibiting ubiquitination. The pharmaceutical compositions can be used in treating various conditions

where ubiquitination is involved. They can also be used as research tools to study the role of ubiquitin in various natural and pathological processes.

[0010] In a first aspect, the invention comprises compounds that inhibit ubiquitination of target proteins.

[0011] In a second aspect, the invention comprises a pharmaceutical composition comprising an inhibitor of ubiquitination according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent.

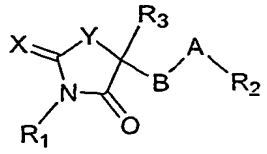
[0012] In a third aspect, the invention comprises methods of inhibiting ubiquitination in a cell, comprising contacting a cell in which inhibition of ubiquitination is desired with a pharmaceutical composition comprising a ubiquitin agent inhibitor according to the invention.

[0013] In a fourth aspect, the invention provides methods for treating cell proliferative diseases or conditions, comprising administering to a patient in need thereof a pharmaceutical composition comprising an effective amount of a ubiquitin agent inhibitor according to the invention.

[0014] The foregoing only summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below. All patent applications and publications of any sort referred to in this specification are hereby incorporated by reference in their entirety. In the event of a discrepancy between the express disclosure of this specification and a patent application or publication incorporated by reference, the express disclosure of this specification shall control.

DETAILED DESCRIPTION OF THE INVENTION

[0015] The first aspect of the invention comprises compounds having the formula



I

or pharmaceutically acceptable salts thereof, wherein

A is aryl or heteroaryl;

B is C_1-C_6 alkyl or C_2-C_6 alkenyl;

X is sulfur, oxygen, $=CR_4R_5$, $=NR_4$, $=NC(O)R_4$, or $=NSO_2R_4$;

Y is sulfur, oxygen, $-C(R_4)(R_5)-$, $-N(R_4)-$, $-NC(O)(R_4)-$, $-NSO_2(R_4)-$, $-S(O)_2-$, or $-S(O)-$;

R_1 is -H, $-NH_2$, C_1-C_6 alkyl, C_1-C_2 alkenyl, C_1-C_6 alkyl-S-C_1-C_6 alkyl, C_0-C_6 alky-aryl, C_0-C_6 alkyl-C(O)OR_6, C_0-C_6 alkyl-heteroaryl, C_0-C_6 alkyl-heterocyclyl, C_0-C_6 alkyl-carbocyclyl, -NH-SO_2-aryl, -C_0-C_6 alkyl-C(O)NR_6R_7, -C_0-C_6 alkyl-C(S)NR_6R_7, C_0-C_6 alky-heteroaryl-aryl, -NHC(O)-aryl, C_0-C_6 alkyl-C(O)NH-C_0-C_6 alkyl-C(O)-O-R_6, C_0-C_6 alkyl-C(O)-NH-C_0-C_6 alkyl-aryl, C_0-C_6 alkyl-C(O)-NH-C_0-C_6 alkyl-heteroaryl, C_0-C_6 alkyl-C(O)-NH-C_0-C_6 alkyl-heterocyclyl, C_0-C_6 alkyl-C(O)-NH-C_0-C_6 alkyl-carbocyclyl, -SO_2-R_6, C(O)-R_6, or -C(O)-OR_6, wherein each one of the alkyl, aryl, heteroaryl, heterocyclic and carbocyclyl are optionally substituted with one or more R_5;

R_2 is -H, halogen, C_1-C_6 alkyl, C_0-C_6 alky-aryl, $-NO_2$, C_0-C_6 alkyl-C(O)-OR_6, C_0-C_6 alkyl-heteroaryl, C_0-C_6 alkyl-heterocyclyl, C_0-C_6 alkyl-carbocyclyl, -N(R_6)-C(O)NR_6R_7,-$NHSO_2$-aryl, C_0-C_6 alky-heteroaryl-aryl, or -C(O)-R_6, wherein each one of the aryl, heteroaryl, heterocyclic and carbocyclyl are optionally substituted with one or more R_4;

R_3 is -H, C_1-C_6 alkyl or C_2-C_6 alkenyl; or

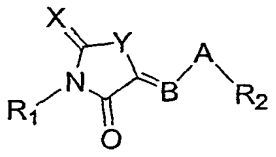
R_3 and B together with the carbon atom to which they are attached form an alkenyl or a spirocyclic ring;

R_4 is halogen, oxo, -C(O)OR_6, $-NO_2$, C_1-C_6 alkyl optionally substituted with halo, -C_1-C_6 alkoxy optionally substituted with halo, $-CH_3$, $-SO_2NH_2$, or -C(O)-OR_6;

R_5 is halogen, oxo, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_0-C_6 alkyl-aryl, $-NO_2$, di(C_1-C_6 alkyl)amino, $-CF_3$, -OH, $-SO_2NH_2$, or -C(O)-OR_6; and

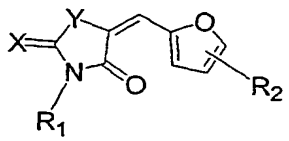
R_6 and R_7 are independently -H, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, aryl, di(C_1-C_6 alkyl)amino, $-CF_3$, -OH, or -C(O)-OR_6.

[0016] In a preferred embodiment, the invention also comprises compounds of paragraph [0015] having the formula



II.

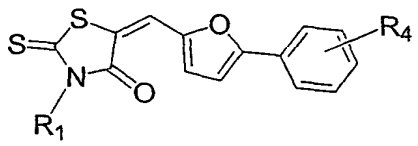
[0017] In another preferred embodiment, the invention further comprises compounds of paragraph [0016] of the formula



III.

[0018] In a preferred embodiment of the invention the compounds of formula III are compounds wherein R_1 is -H, C_1-C_6 alkyl, C_1-C_2 alkenyl, C_0-C_6 alky-aryl, C_0-C_6 alkyl-C(O)OR_6, C_0-C_6 alkyl-heteroaryl, C_0-C_6 alkyl-heterocyclyl, C_0-C_6 alkyl-carbocyclyl or C_0-C_6 alky-heteroaryl-aryl, and R_2 is -H, halogen, C_1-C_6 alkyl or C_0-C_6 alky-aryl. More preferably, R_1 is -H, C_1-C_6 alkyl, C_1-C_2 alkenyl, C_0-C_6 alky-aryl, or C_0-C_6 alkyl-C(O)OR_6 and R_2 is C_0-C_6 alky-aryl. Even more preferably, R_1 is -H, allyl, phenyl or benzyl, and R_2 is phenyl.

[0019] In another preferred embodiment, the invention also comprises compounds of paragraph [0017] of the formula



IV.

[0020] Preferably, the compounds of formula IV are compounds wherein R_1 is -H, C_1-C_6 alkyl, C_1-C_2 alkenyl, C_0-C_6 alky-aryl, C_0-C_6 alkyl-C(O)OR_6, C_0-C_6 alkyl-heteroaryl, C_0-C_6 alkyl-heterocyclyl, C_0-C_6 alkyl-carbocyclyl or C_0-C_6 alky-heteroaryl-aryl, and R_4 is halogen, oxo, -NO_2, C_1-C_6 alkyl, -C_1-C_6 alkoxy, -CF_3, -SO_2NH_2 or -C(O)-OR_6. More preferably, R_1 is -H, C_1-C_6 alkyl, C_1-C_2 alkenyl, C_0-C_6 alky-aryl or C_0-C_6 alkyl-C(O)OR_6, and R_4 is halogen, -NO_2, C_1-C_6 alkyl, -C_1-C_6 alkoxy, -CF_3, -SO_2NH_2 or -C(O)-OR_6. Even more preferably, R_1 is -H, allyl, phenyl or benzyl, and R_4 is chloro, bromo, fluoro, -NO_2, -OCH_3, -CF_3 or -C(O)-OH.

[0021] In another embodiment, the invention comprises compounds of paragraph [0015] or [0016] that are not also compounds of any of paragraphs [0017] – [0020].

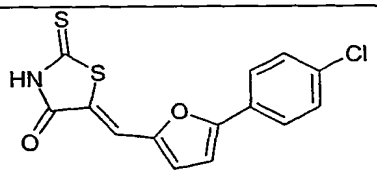
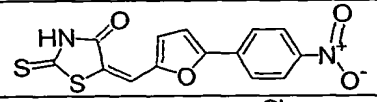
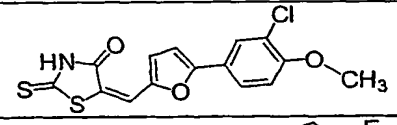
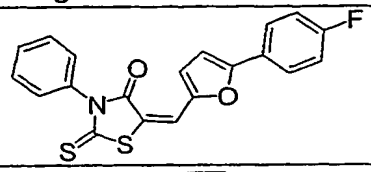
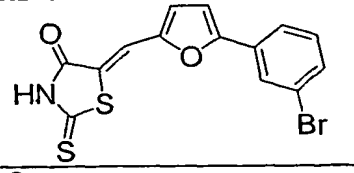
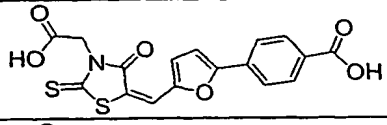
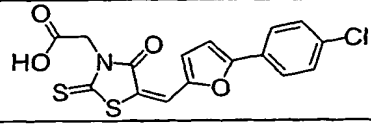
[0022] The second aspect of the invention comprises pharmaceutical compositions comprising a pharmaceutically acceptable carrier, diluent or excipient, and a compound of formula I as described in any one of paragraphs [0015] - [0021].

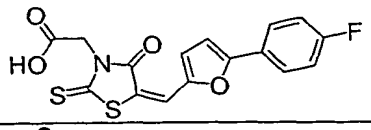
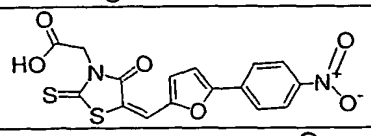
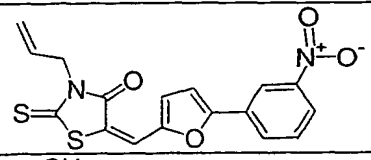
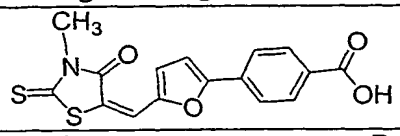
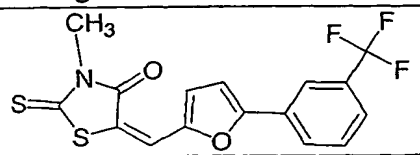
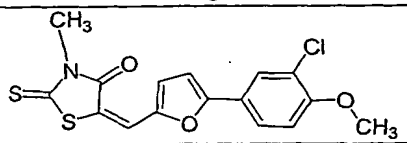
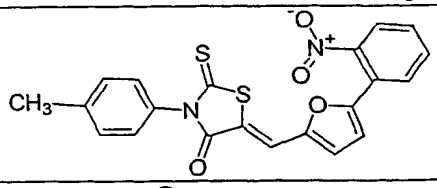
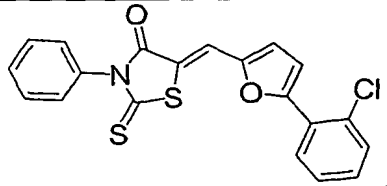
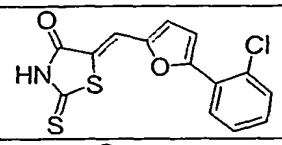
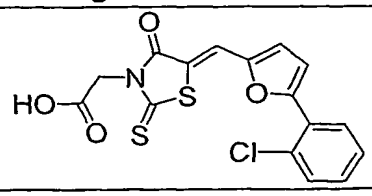
[0023] The compounds and pharmaceutical compositions of the invention are useful as inhibitors of ubiquitination because they inhibit ubiquitin agents that are the enzymes involved in the ubiquitination pathway. Specifically, the compounds and compositions of the invention inhibit the ubiquitin ligating activity of the E3 enzyme. Inhibition of the E3 enzyme also decreases the upstream functions of the E1 (ubiquitin activation with ATP) and E2 (transfer of activated ubiquitin to E3) enzymes. Accordingly, the compounds and compositions of the invention are useful for the inhibition of ubiquitination in a cell or in a patient suffering from a disease or condition that involves ubiquitination.

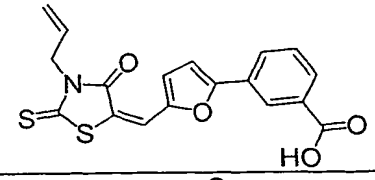
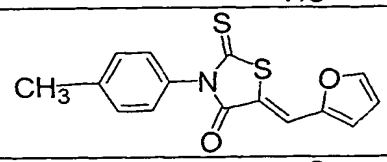
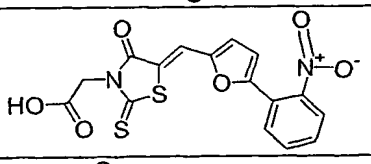
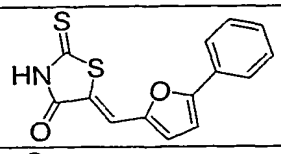
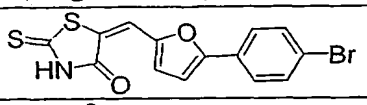
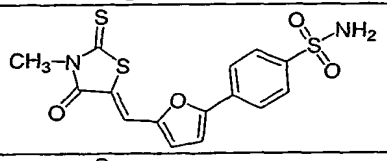
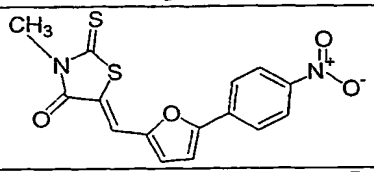
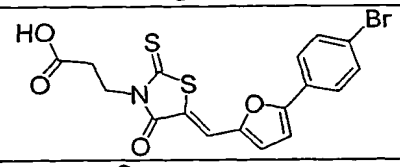
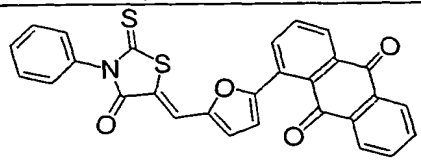
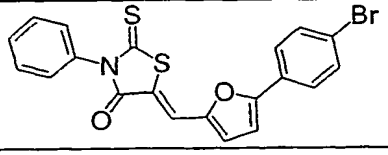
[0024] Thus, the third aspect of the invention comprises methods of inhibiting ubiquitination in a cell, comprising contacting a cell in which inhibition of ubiquitination is desired with a compound or pharmaceutical composition comprising a ubiquitin agent inhibitor according to the invention.

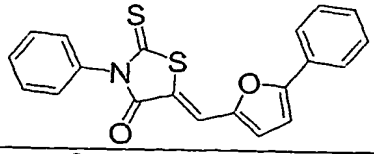
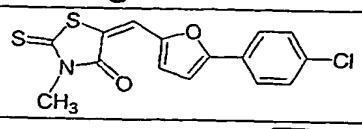
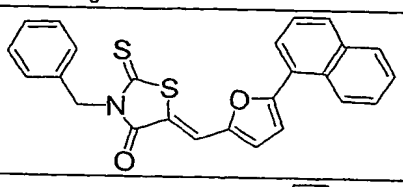
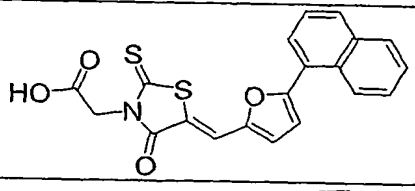
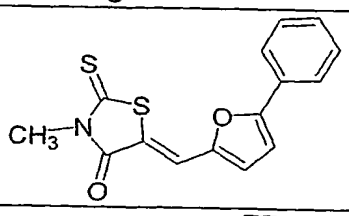
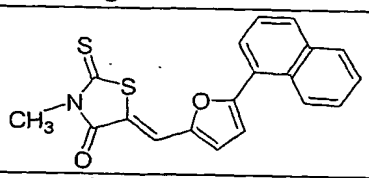
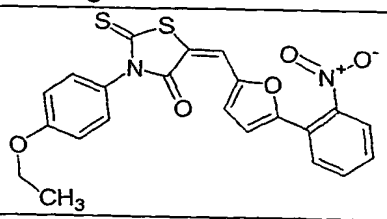
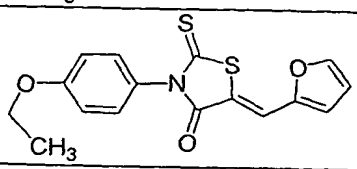
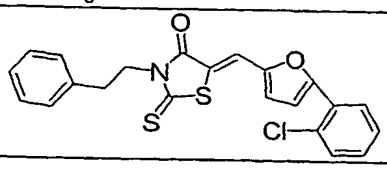
[0025] The fourth aspect of the invention comprises methods for treating cell proliferative diseases or conditions, comprising administering to a patient in need thereof a pharmaceutical composition comprising an effective amount of a ubiquitin agent inhibitor according to the invention. For example, diseases and conditions that can be treated are all types of cancers and conditions related to cancers. However, any disease or condition in which ubiquitination is a component can be treated with the compounds and pharmaceutical compositions of the invention.

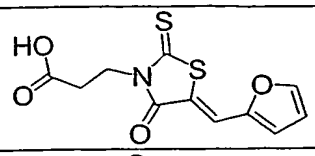
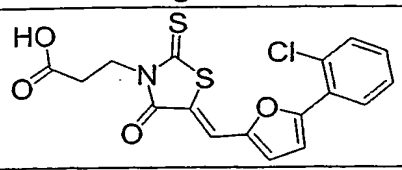
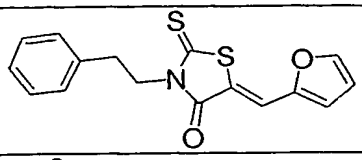
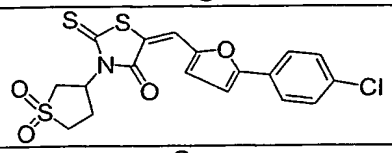
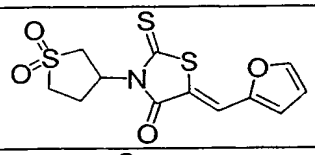
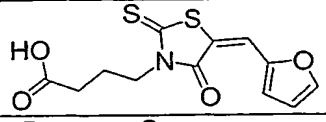
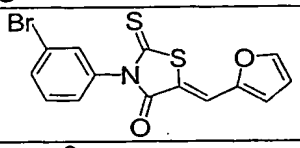
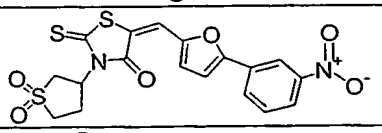
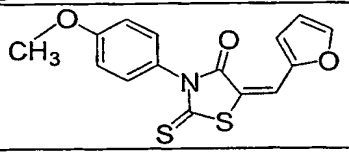
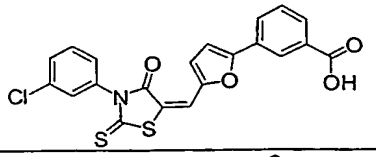
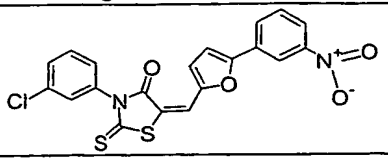
[0026] The table below illustrates certain preferred embodiments of the first aspect of the invention. We have found that the compounds listed in the table are useful as inhibitors of ubiquitinization, as described more fully below, and, accordingly, useful as anti-cancer agents.

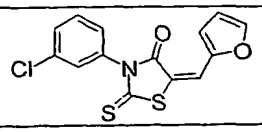
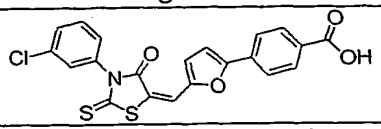
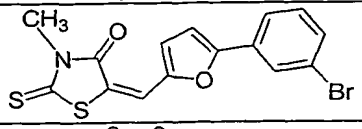
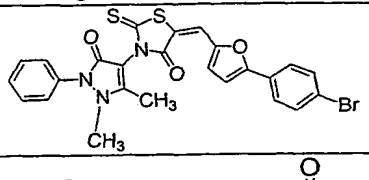
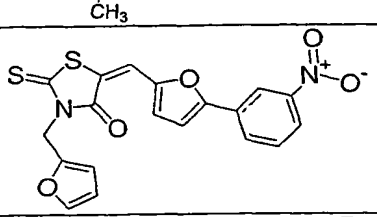
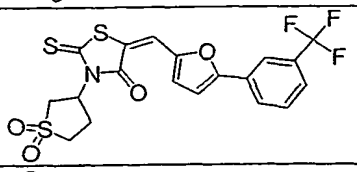
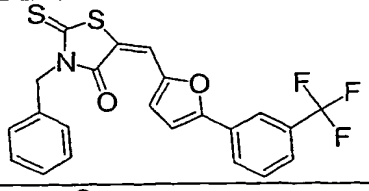
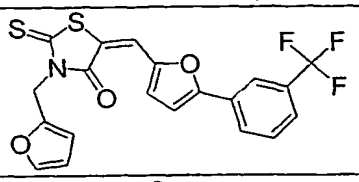
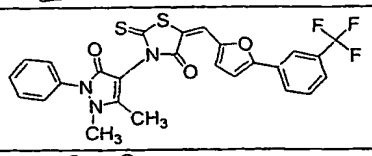
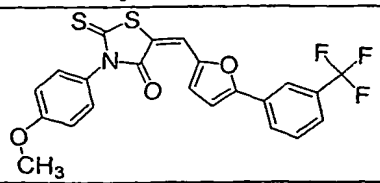
Cpd	Structure	Name
1		(5*Z*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
2		(5*E*)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
3		(5*E*)-5-{[5-(3-chloro-4-methoxyphenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
4		(5*E*)-5-{[5-(4-fluorophenyl)-2-furyl]methylene}-3-phenyl-2-thioxo-1,3-thiazolidin-4-one
5		(5*Z*)-5-{[5-(3-bromophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
6		4-(5-{(*E*)-[3-(carboxymethyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid
7		((5*E*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid

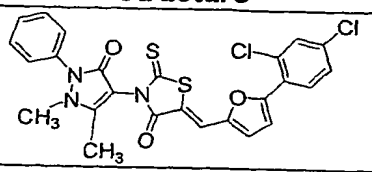
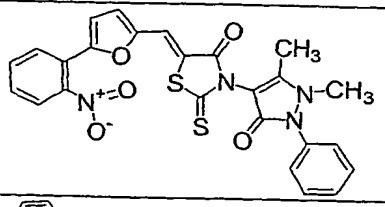
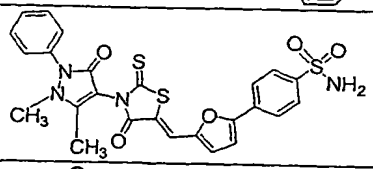
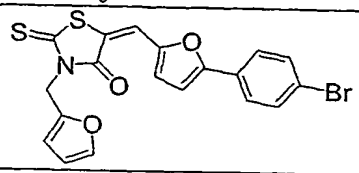
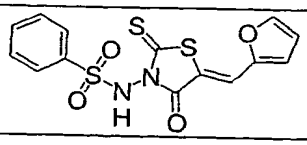
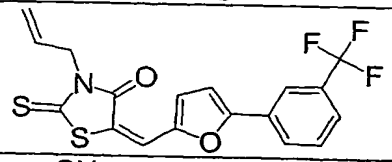
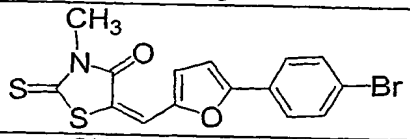
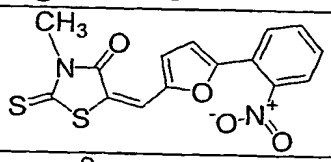
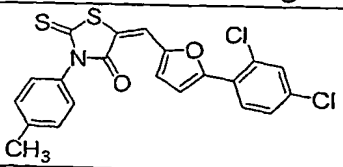
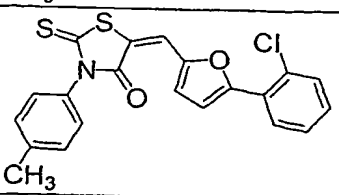
Cpd	Structure	Name
8		((5*E*)-5-{[5-(4-fluorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
9		((5*E*)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
10		(5*E*)-3-allyl-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
11		4-{5-[(*E*)-(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid
12		(5*E*)-3-methyl-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one
13		(5*E*)-5-{[5-(3-chloro-4-methoxyphenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
14		(5*Z*)-3-(4-methylphenyl)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
15		(5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-phenyl-2-thioxo-1,3-thiazolidin-4-one
16		(5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
17		((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid

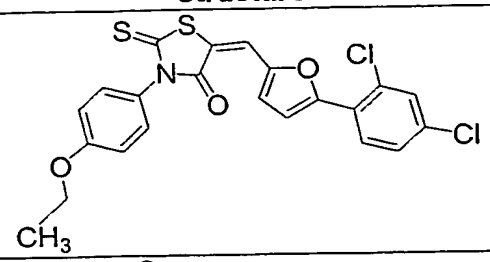
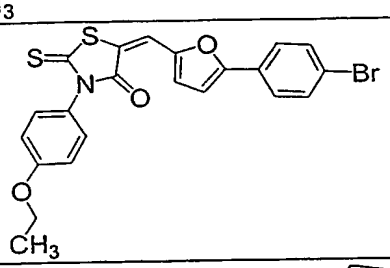
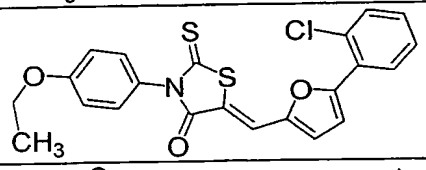
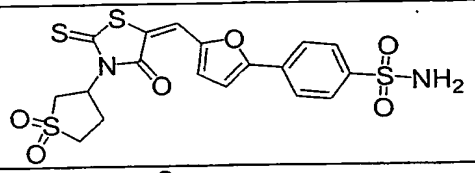
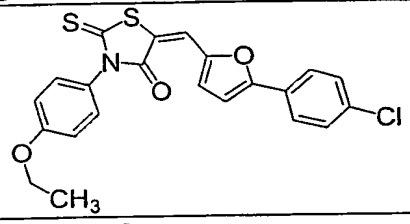
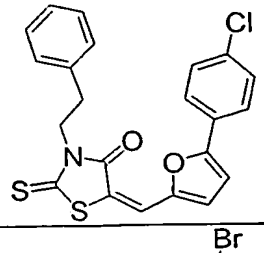
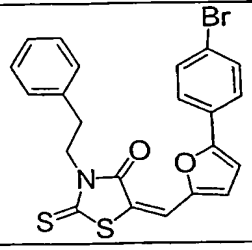
Cpd	Structure	Name
18		3-{5-[(*E*)-(3-allyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid
19		(5*Z*)-5-(2-furylmethylene)-3-(4-methylphenyl)-2-thioxo-1,3-thiazolidin-4-one
20		((5*Z*)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
21		(5*Z*)-5-[(5-phenyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
22		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
23		4-{5-[(*Z*)-(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzenesulfonamide
24		(5*Z*)-3-methyl-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
25		3-((5*Z*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
26		1-{5-[(*Z*)-(4-oxo-3-phenyl-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}anthra-9,10-quinone
27		(5*Z*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-phenyl-2-thioxo-1,3-thiazolidin-4-one

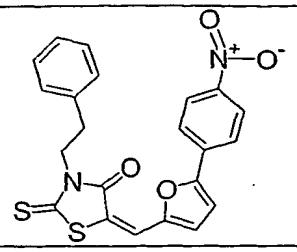
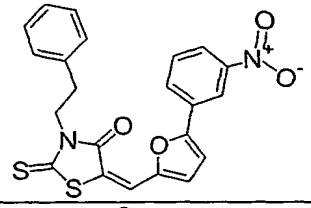
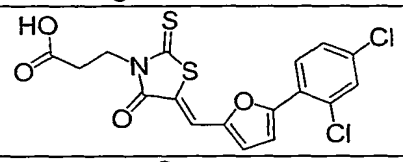
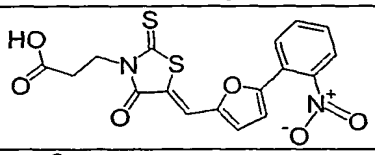
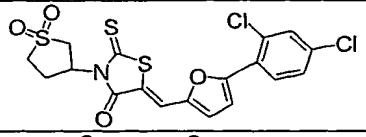
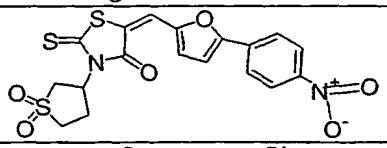
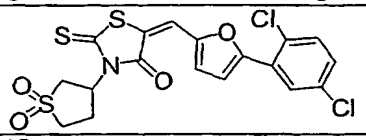
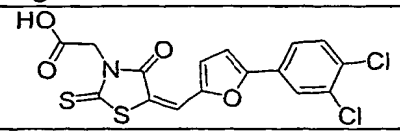
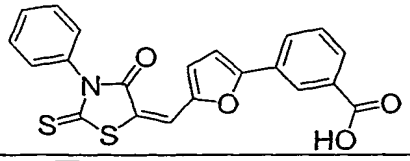
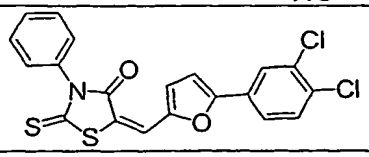
Cpd	Structure	Name
28		(5Z)-3-phenyl-5-[(5-phenyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
29		(5E)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
30		(5Z)-3-benzyl-5-{[5-(1-naphthyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
31		((5Z)-5-{[5-(1-naphthyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
32		(5Z)-3-methyl-5-[(5-phenyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
33		(5Z)-3-methyl-5-{[5-(1-naphthyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
34		(5E)-3-(4-ethoxyphenyl)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
35		(5Z)-3-(4-ethoxyphenyl)-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
36		(5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-4-one

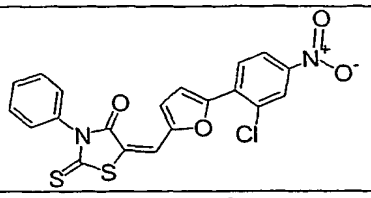
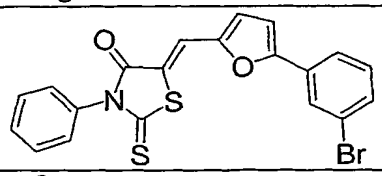
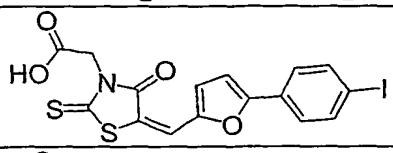
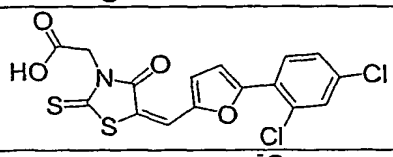
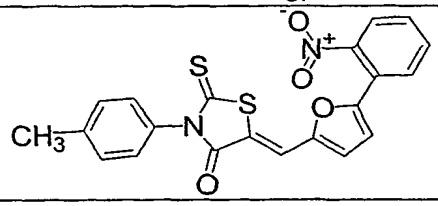
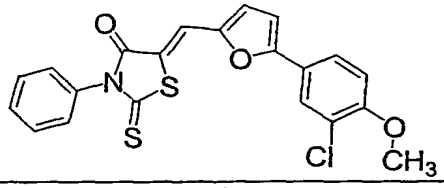
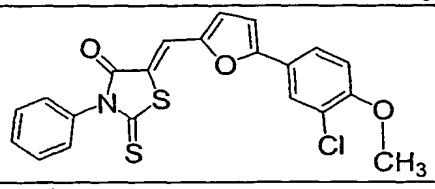
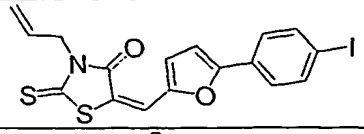
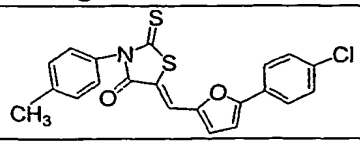
Cpd	Structure	Name
37		3-[(5*Z*)-5-(2-furylmethylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]propanoic acid
38		3-((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
39		(5*Z*)-5-(2-furylmethylene)-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-4-one
40		(5*E*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
41		(5*Z*)-3-(1,1-dioxidotetrahydro-3-thienyl)-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
42		4-[(5*E*)-5-(2-furylmethylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]butanoic acid
43		(5*Z*)-3-(3-bromophenyl)-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
44		(5*E*)-3-(1,1-dioxidotetrahydro-3-thienyl)-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
45		(5*E*)-5-(2-furylmethylene)-3-(4-methoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one
46		3-(5-{(*E*)-[3-(3-chlorophenyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid
47		(5*E*)-3-(3-chlorophenyl)-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

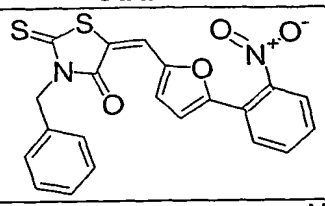
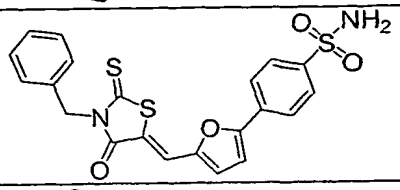
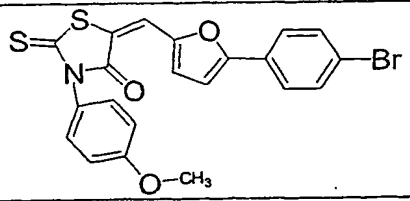
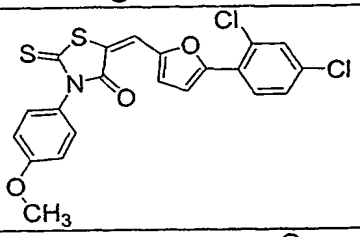
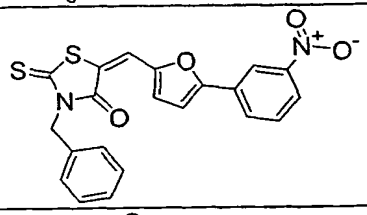
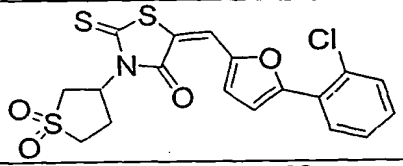
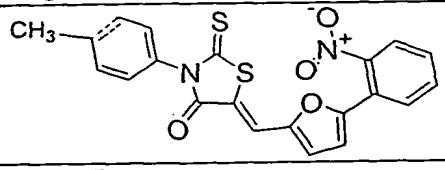
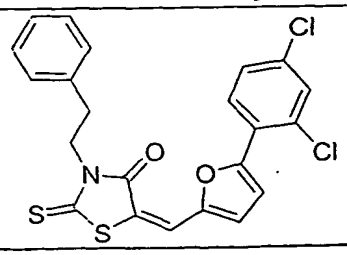
Cpd	Structure	Name
48		(5*E*)-3-(3-chlorophenyl)-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
49		4-(5-{(*E*)-[3-(3-chlorophenyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid
50		(5*E*)-5-{[5-(3-bromophenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
51		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxo-1,3-thiazolidin-4-one
52		(5*E*)-3-(2-furylmethyl)-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
53		(5*E*)-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one
54		(5*E*)-3-benzyl-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one
55		(5*E*)-3-(2-furylmethyl)-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one
56		(5*E*)-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one
57		(5*E*)-3-(4-methoxyphenyl)-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one

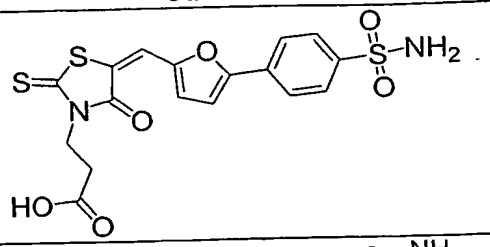
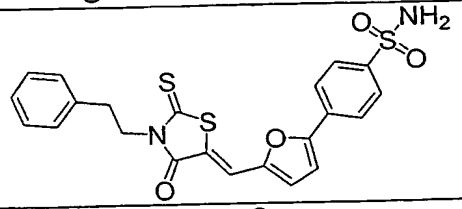
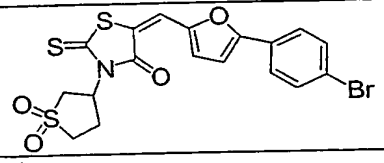
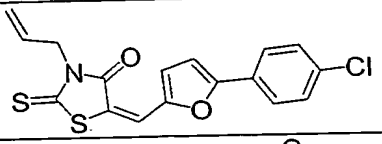
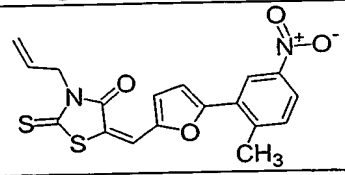
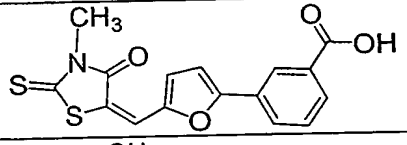
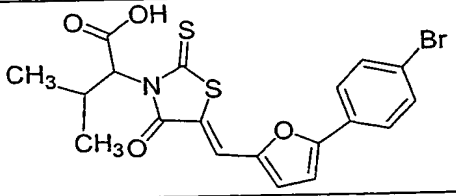
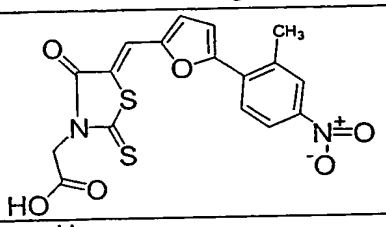
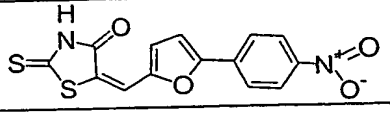
Cpd	Structure	Name
58		(5*Z*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxo-1,3-thiazolidin-4-one
59		(5*Z*)-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
60		4-(5-{(*Z*)-[3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzenesulfonamide
61		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-(2-furylmethyl)-2-thioxo-1,3-thiazolidin-4-one
62		*N*-[(5*Z*)-5-(2-furylmethylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]benzenesulfonamide
63		(5*E*)-3-allyl-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one
64		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
65		(5*E*)-3-methyl-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
66		(5*E*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-3-(4-methylphenyl)-2-thioxo-1,3-thiazolidin-4-one
67		(5*E*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(4-methylphenyl)-2-thioxo-1,3-thiazolidin-4-one

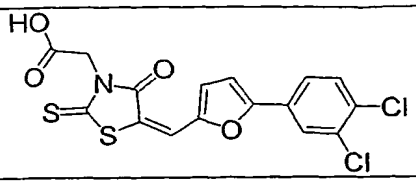
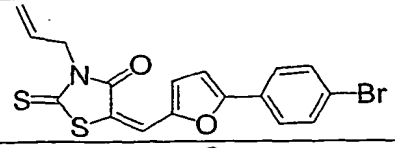
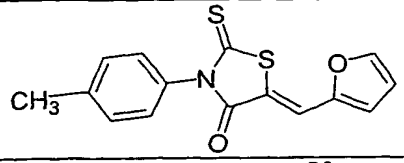
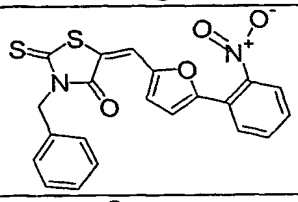
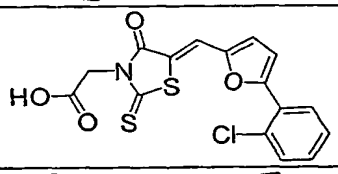
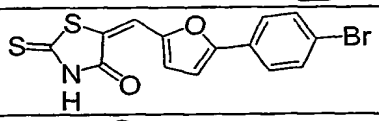
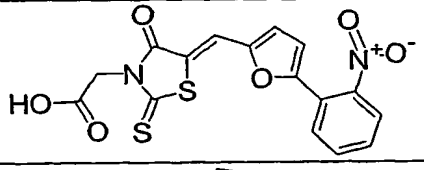
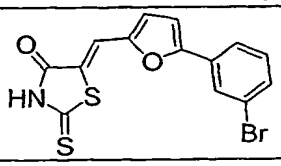
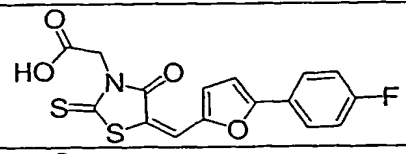
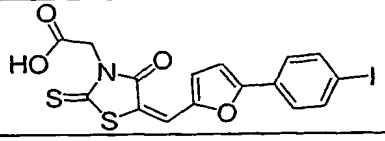
Cpd	Structure	Name
68		(5*E*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-3-(4-ethoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one
69		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-(4-ethoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one
70		(5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(4-ethoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one
71		4-(5-{(*E*)-[3-(1,1-dioxidotetrahydro-3-thienyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzenesulfonamide
72		(5*E*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-3-(4-ethoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one
73		(5*E*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-4-one
74		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-4-one

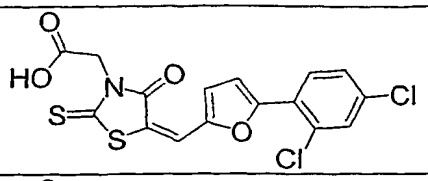
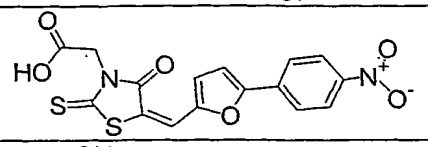
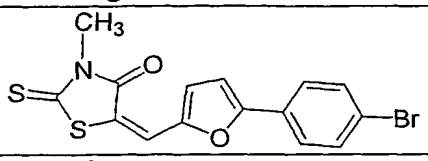
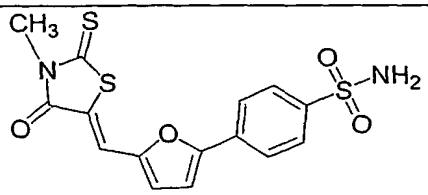
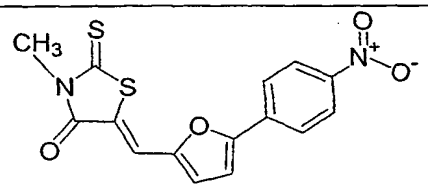
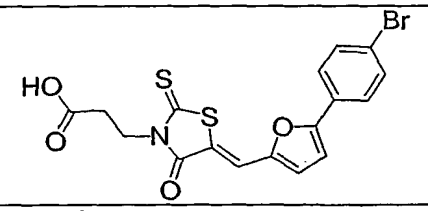
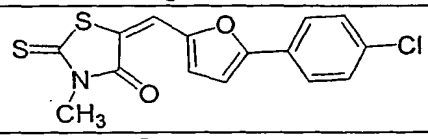
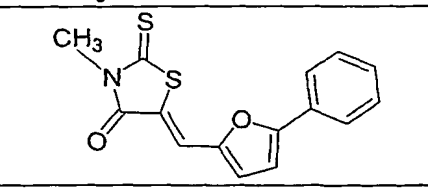
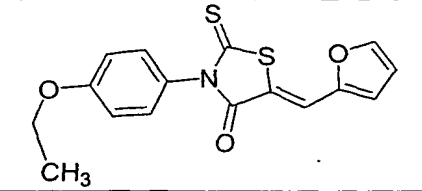
Cpd	Structure	Name
75		(5*E*)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-4-one
76		(5*E*)-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-4-one
77		3-((5*Z*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
78		3-((5*Z*)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
79		(5*Z*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
80		(5*E*)-3-(1,1-dioxidotetrahydro-3-thienyl)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
81		(5*E*)-5-{[5-(2,5-dichlorophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
82		((5*E*)-5-{[5-(3,4-dichlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
83		3-{5-[(*E*)-(4-oxo-3-phenyl-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid
84		(5*E*)-5-{[5-(3,4-dichlorophenyl)-2-furyl]methylene}-3-phenyl-2-thioxo-1,3-thiazolidin-4-one

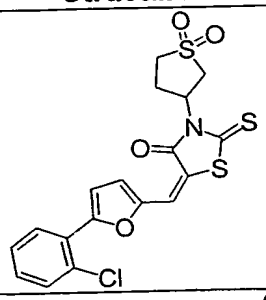
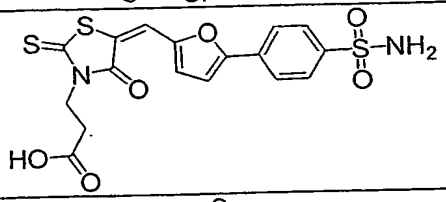
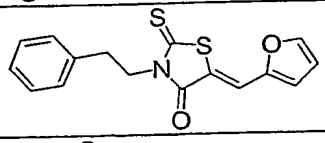
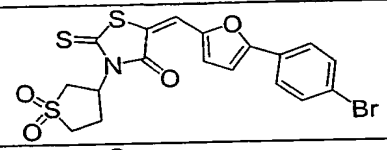
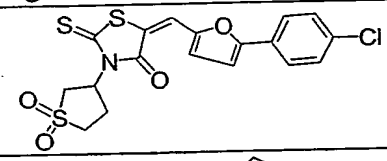
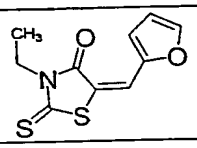
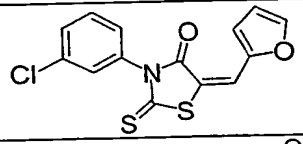
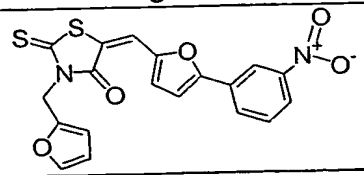
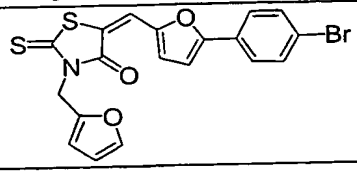
Cpd	Structure	Name
85		(5*E*)-5-{[5-(2-chloro-4-nitrophenyl)-2-furyl]methylene}-3-phenyl-2-thioxo-1,3-thiazolidin-4-one
86		(5*Z*)-5-{[5-(3-bromophenyl)-2-furyl]methylene}-3-phenyl-2-thioxo-1,3-thiazolidin-4-one
87		((5*E*)-5-{[5-(4-iodophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
88		((5*E*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
89		(5*Z*)-3-(4-methylphenyl)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
90		(5*Z*)-5-{[5-(3-chloro-4-methoxyphenyl)-2-furyl]methylene}-3-phenyl-2-thioxo-1,3-thiazolidin-4-one
91		(5*Z*)-5-{[5-(3-chloro-4-methoxyphenyl)-2-furyl]methylene}-3-phenyl-2-thioxo-1,3-thiazolidin-4-one
92		(5*E*)-3-allyl-5-{[5-(4-iodophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
93		(5*Z*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-3-(4-methylphenyl)-2-thioxo-1,3-thiazolidin-4-one

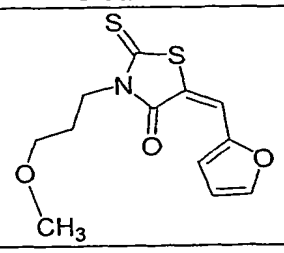
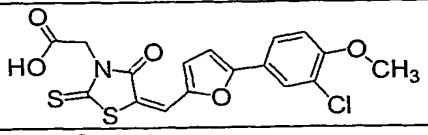
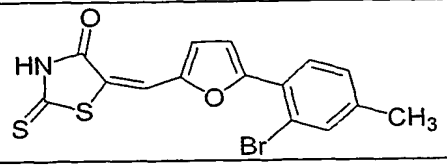
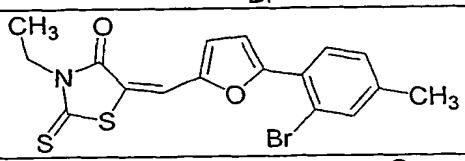
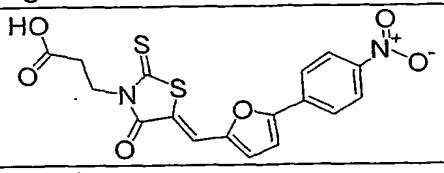
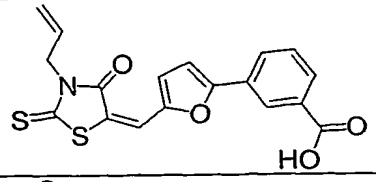
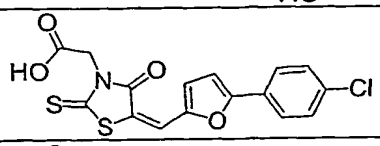
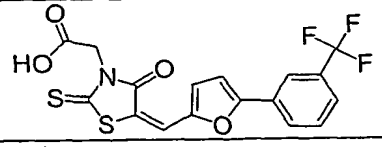
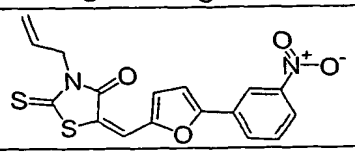
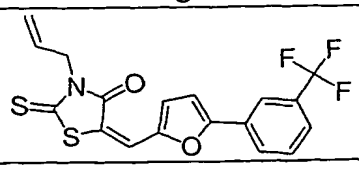
Cpd	Structure	Name
94		(5*E*)-3-benzyl-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
95		4-{5-[(*Z*)-(3-benzyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzenesulfonamide
96		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-(4-methoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one
97		(5*E*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-3-(4-methoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one
98		(5*E*)-3-benzyl-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
99		(5*E*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
100		(5*Z*)-3-(4-methylphenyl)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
101		(5*E*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-4-one

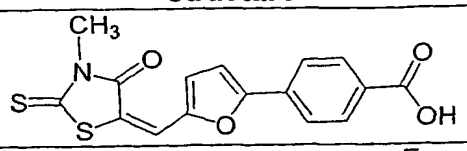
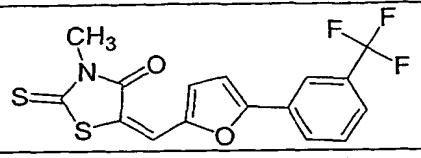
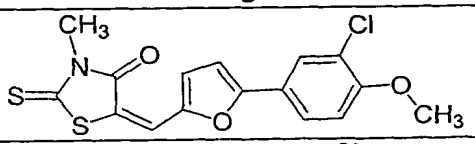
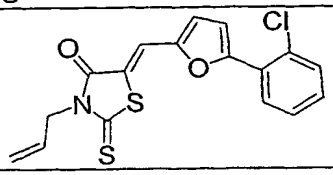
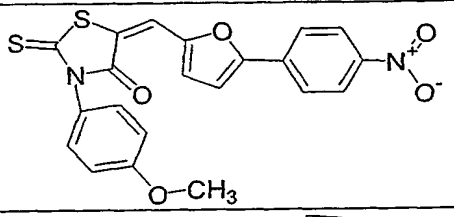
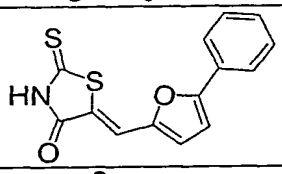
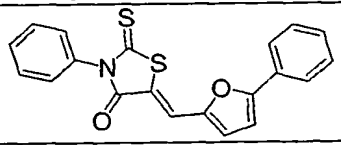
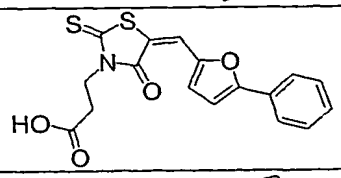
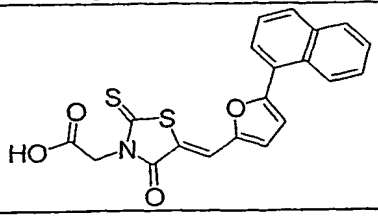
Cpd	Structure	Name
102		3-[(5*E*)-5-({5-[4-(aminosulfonyl)phenyl]-2-furyl}methylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]propanoic acid
103		4-(5-{(*Z*)-[4-oxo-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzenesulfonamide
104		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
105		(5*E*)-3-allyl-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
106		(5*E*)-3-allyl-5-{[5-(2-methyl-5-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
107		3-{5-[(*E*)-(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid
108		2-((5*Z*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-3-methylbutanoic acid
109		((5*Z*)-5-{[5-(2-methyl-4-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
110		(5*E*)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

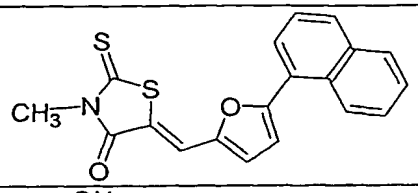
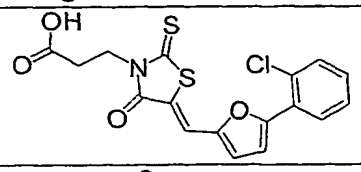
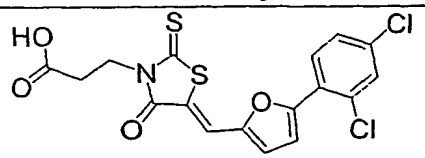
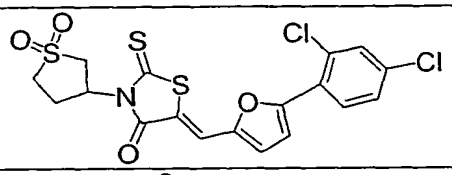
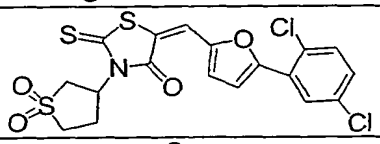
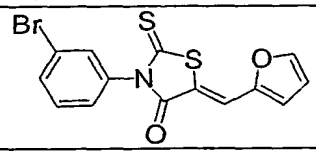
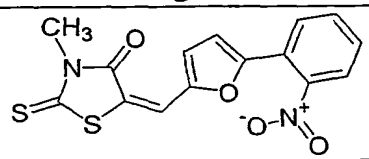
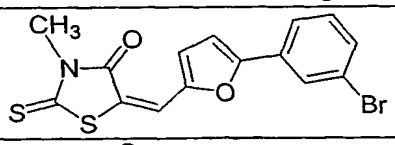
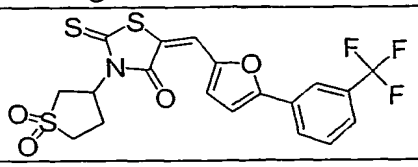
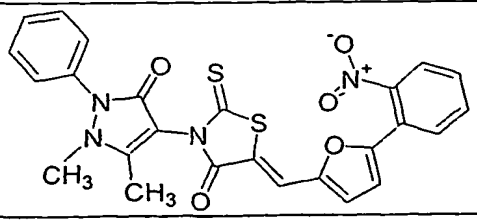
Cpd	Structure	Name
111		((5*E*)-5-{[5-(3,4-dichlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
112		(5*E*)-3-allyl-5-{[5-(4-bromophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
113		(5*Z*)-5-(2-furylmethylene)-3-(4-methylphenyl)-2-thioxo-1,3-thiazolidin-4-one
114		(5*E*)-3-benzyl-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
115		((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
116		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
117		((5*Z*)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
118		(5*Z*)-5-{[5-(3-bromophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
119		((5*E*)-5-{[5-(4-fluorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
120		((5*E*)-5-{[5-(4-iodophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid

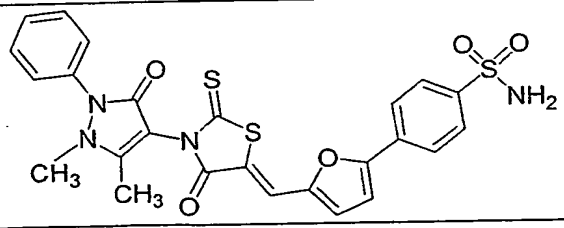
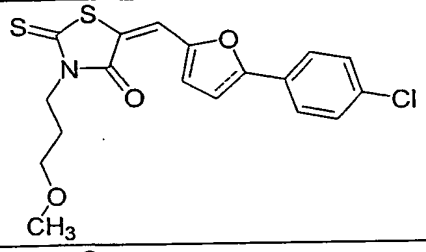
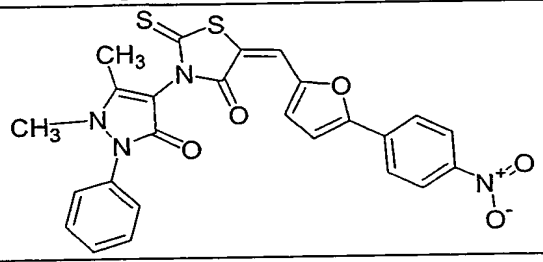
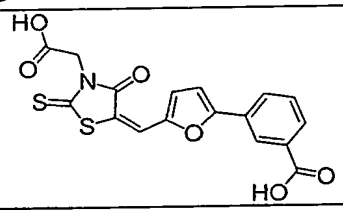
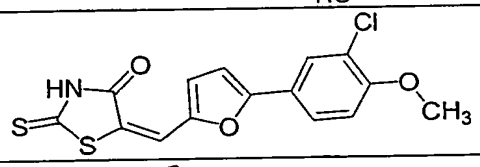
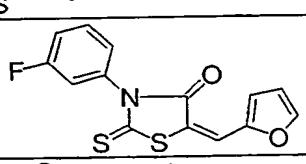
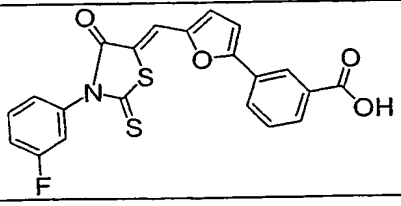
Cpd	Structure	Name
121		((5*E*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
122		((5*E*)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
123		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
124		4-{5-[(*Z*)-(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzenesulfonamide
125		(5*Z*)-3-methyl-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
126		3-((5*Z*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
127		(5*E*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
128		(5*Z*)-3-methyl-5-[(5-phenyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
129		(5*Z*)-3-(4-ethoxyphenyl)-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one

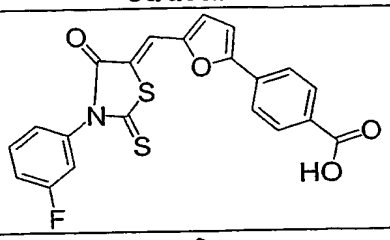
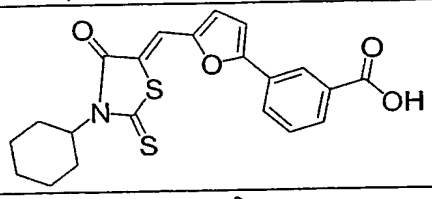
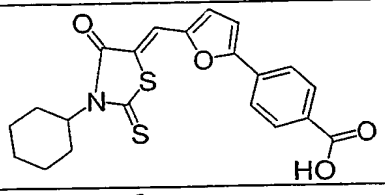
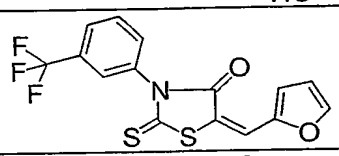
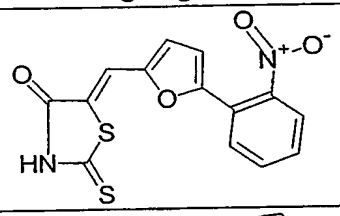
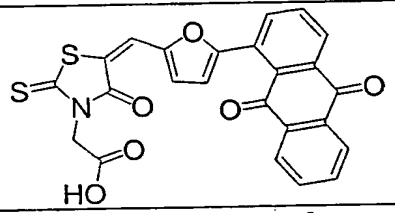
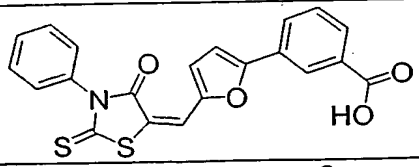
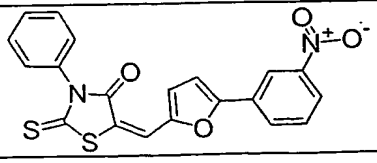
Cpd	Structure	Name
130		(5*E*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
131		3-[(5*E*)-5-({5-[4-(aminosulfonyl)phenyl]-2-furyl}methylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]propanoic acid
132		(5*Z*)-5-(2-furylmethylene)-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-4-one
133		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
134		(5*E*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
135		(5*E*)-3-ethyl-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
136		(5*E*)-3-(3-chlorophenyl)-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
137		(5*E*)-3-(2-furylmethyl)-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
138		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-(2-furylmethyl)-2-thioxo-1,3-thiazolidin-4-one

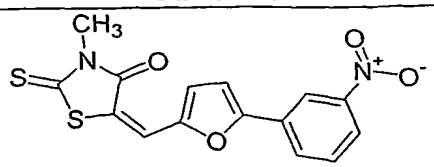
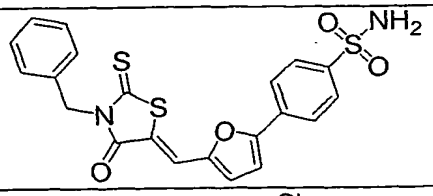
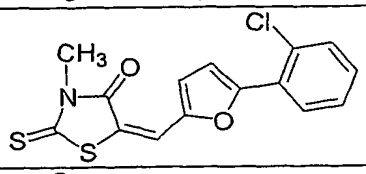
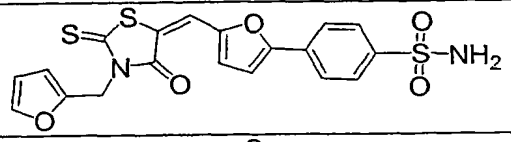
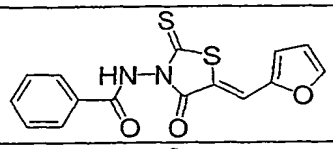
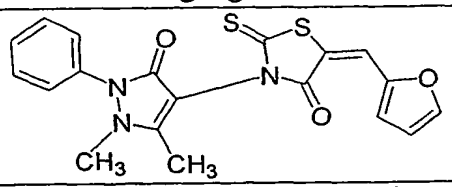
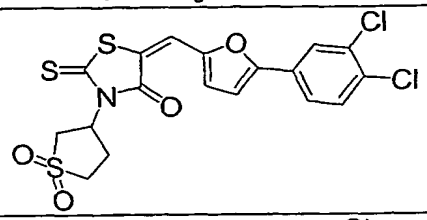
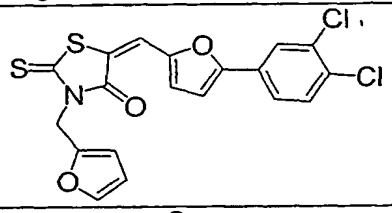
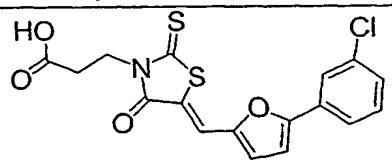
Cpd	Structure	Name
139		(5*E*)-5-(2-furylmethylene)-3-(3-methoxypropyl)-2-thioxo-1,3-thiazolidin-4-one
140		((5*E*)-5-{[5-(3-chloro-4-methoxyphenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
141		(5*E*)-5-{[5-(2-bromo-4-methylphenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
142		(5*E*)-5-{[5-(2-bromo-4-methylphenyl)-2-furyl]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one
143		3-((5*Z*)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
144		3-{5-[(*E*)-(3-allyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid
145		((5*E*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
146		[(5*E*)-4-oxo-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-3-yl]acetic acid
147		(5*E*)-3-allyl-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
148		(5*E*)-3-allyl-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one

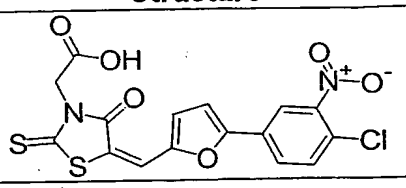
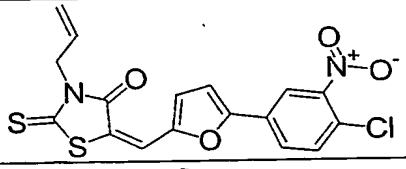
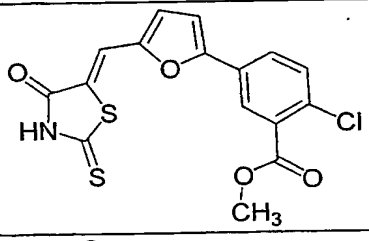
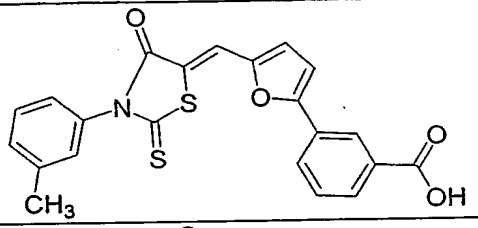
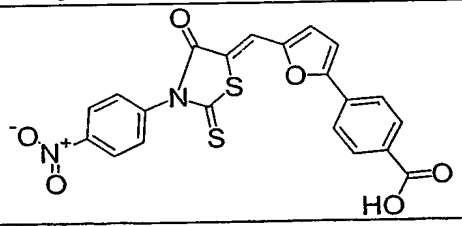
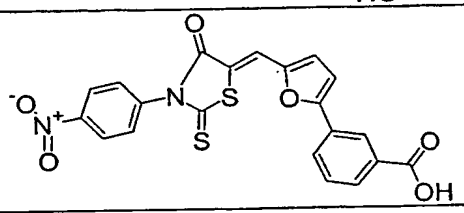
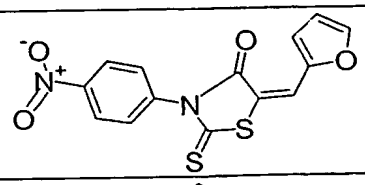
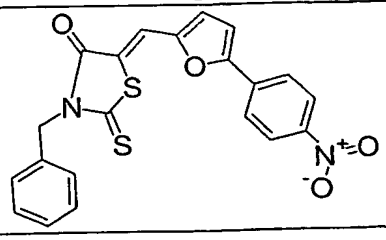
Cpd	Structure	Name
149		4-{5-[(*E*)-(3-methyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid
150		(5*E*)-3-methyl-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one
151		(5*E*)-5-{[5-(3-chloro-4-methoxyphenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
152		(5*Z*)-3-allyl-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
153		(5*E*)-3-(4-methoxyphenyl)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
154		(5*Z*)-5-[(5-phenyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
155		(5*Z*)-3-phenyl-5-[(5-phenyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
156		3-{(5*E*)-4-oxo-5-[(5-phenyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-3-yl}propanoic acid
157		((5*Z*)-5-{[5-(1-naphthyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid

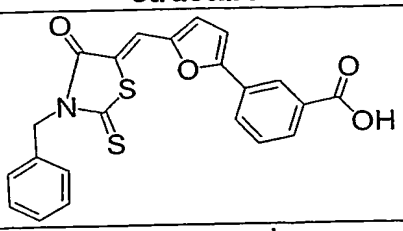
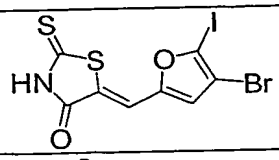
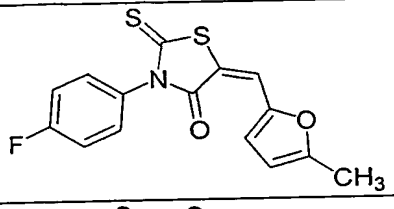
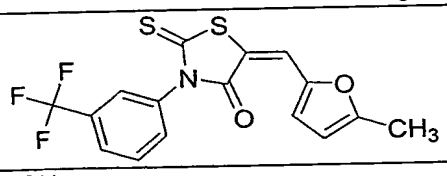
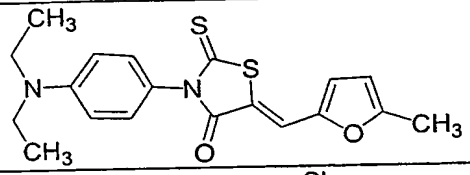
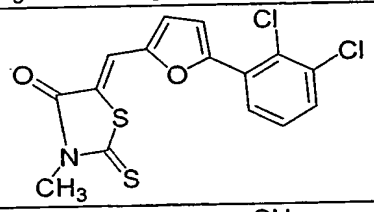
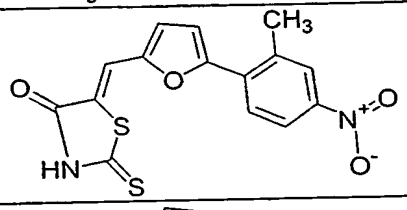
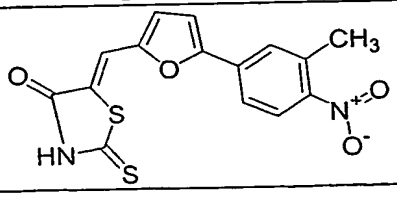
Cpd	Structure	Name
158		(5*Z*)-3-methyl-5-{[5-(1-naphthyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
159		3-((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
160		3-((5*Z*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
161		(5*Z*)-5-{[5-(2,4-dichlorophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
162		(5*E*)-5-{[5-(2,5-dichlorophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
163		(5*Z*)-3-(3-bromophenyl)-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
164		(5*E*)-3-methyl-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
165		(5*E*)-5-{[5-(3-bromophenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
166		(5*E*)-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one
167		(5*Z*)-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

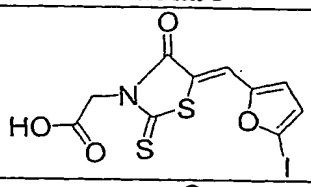
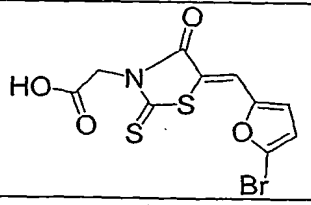
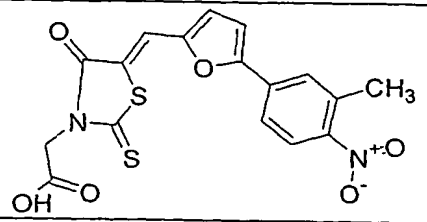
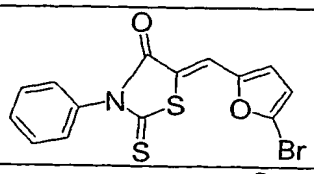
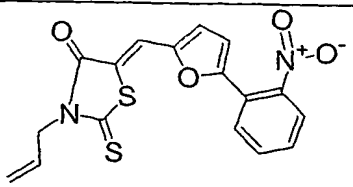
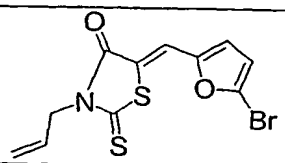
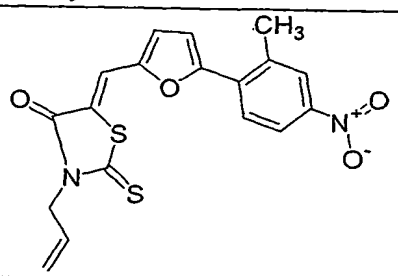
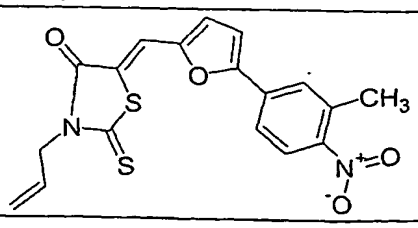
Cpd	Structure	Name
168		4-(5-{(*Z*)-[3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzenesulfonamide
169		(5*E*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-3-(3-methoxypropyl)-2-thioxo-1,3-thiazolidin-4-one
170		(5*E*)-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
171		3-(5-{(*E*)-[3-(carboxymethyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid
172		(5*E*)-5-{[5-(3-chloro-4-methoxyphenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
173		(5*E*)-3-(3-fluorophenyl)-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
174		3-(5-{(*Z*)-[3-(3-fluorophenyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid

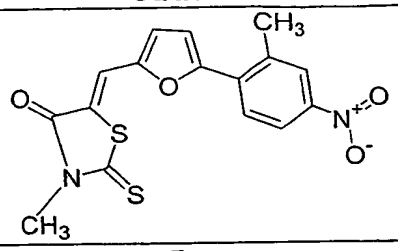
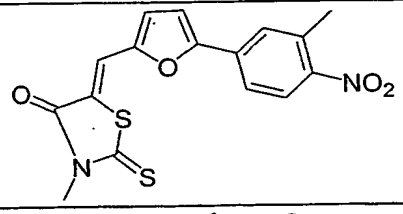
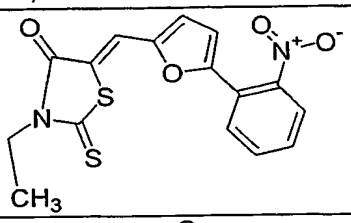
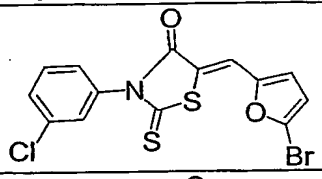
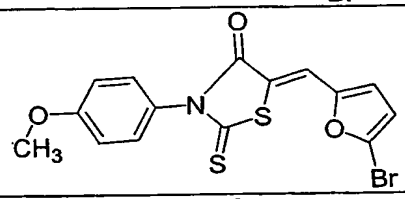
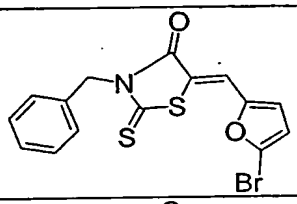
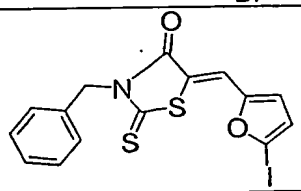
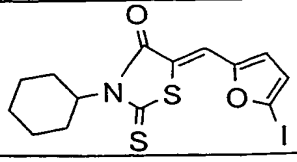
Cpd	Structure	Name
175		4-{5-{(*Z*)-[3-(3-fluorophenyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid
176		3-{5-[(*Z*)-(3-cyclohexyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid
177		4-{5-[(*Z*)-(3-cyclohexyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid
178		(5*E*)-5-(2-furylmethylene)-2-thioxo-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-one
179		(5*Z*)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
180		((5*E*)-5-{[5-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
181		3-{5-[(*E*)-(4-oxo-3-phenyl-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid
182		(5*E*)-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-3-phenyl-2-thioxo-1,3-thiazolidin-4-one

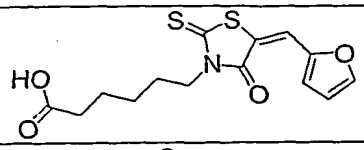
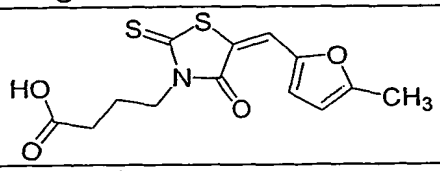
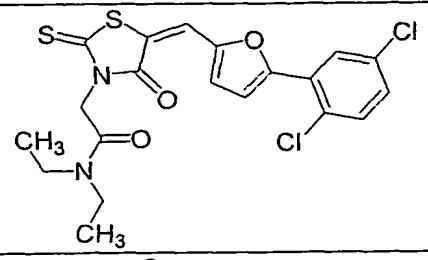
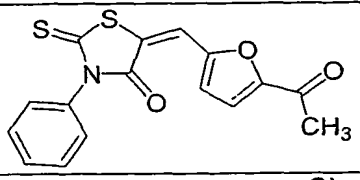
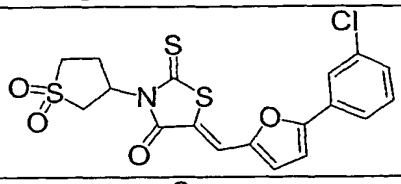
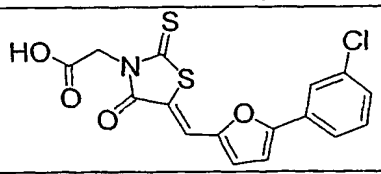
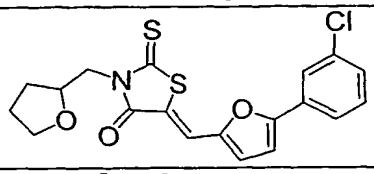
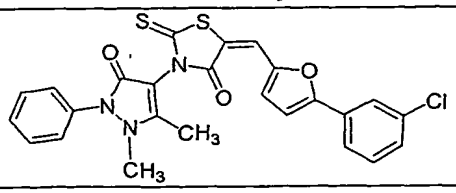
Cpd	Structure	Name
183		(5*E*)-3-methyl-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
184		4-{5-[(*Z*)-(3-benzyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzenesulfonamide
185		(5*E*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
186		4-(5-{(*E*)-[3-(2-furylmethyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzenesulfonamide
187		*N*-[(5*Z*)-5-(2-furylmethylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]benzamide
188		(5*E*)-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
189		(5*E*)-5-{[5-(3,4-dichlorophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
190		(5*E*)-5-{[5-(3,4-dichlorophenyl)-2-furyl]methylene}-3-(2-furylmethyl)-2-thioxo-1,3-thiazolidin-4-one
191		3-((5*Z*)-5-{[5-(3-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid

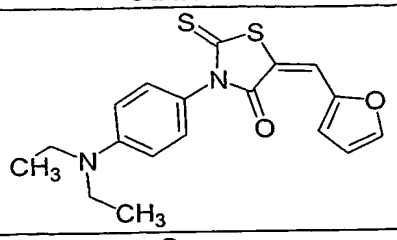
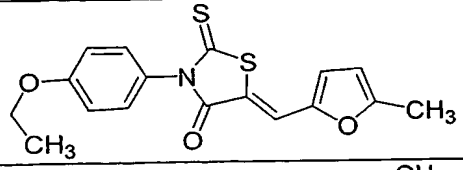
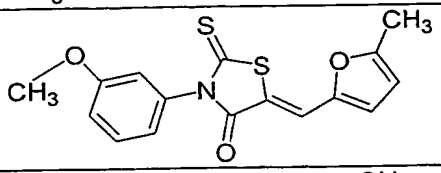
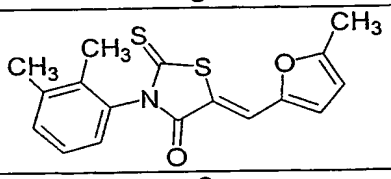
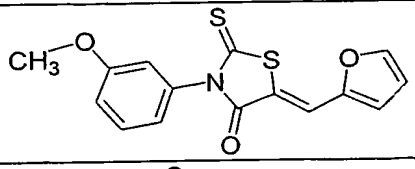
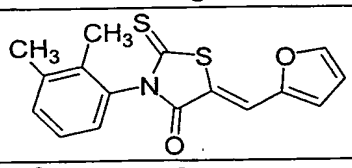
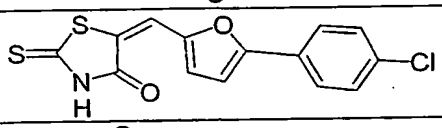
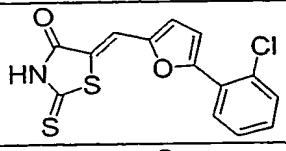
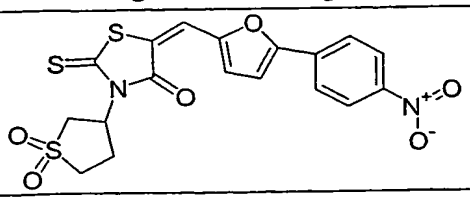
Cpd	Structure	Name
192		((5*E*)-5-{[5-(4-chloro-3-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
193		(5*E*)-5-{[5-(4-chloro-3-nitrophenyl)-2-furyl]methylene}-3-propyl-2-thioxo-1,3-thiazolidin-4-one
194		methyl 2-chloro-5-{5-[(*Z*)-(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoate
195		3-(5-{(*Z*)-[3-(3-methylphenyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid
196		4-(5-{(*Z*)-[3-(4-nitrophenyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid
197		3-(5-{(*Z*)-[3-(4-nitrophenyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzoic acid
198		(5*E*)-5-(2-furylmethylene)-3-(4-nitrophenyl)-2-thioxo-1,3-thiazolidin-4-one
199		(5*Z*)-3-benzyl-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

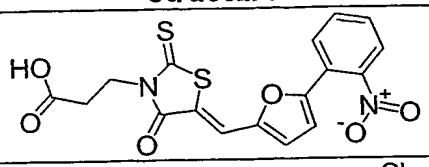
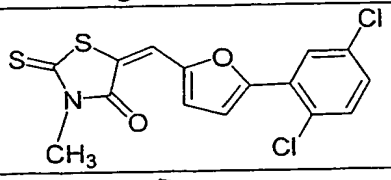
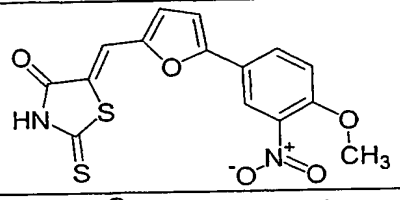
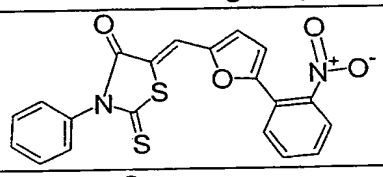
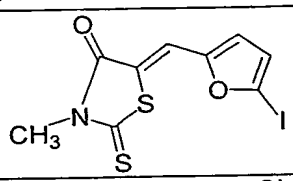
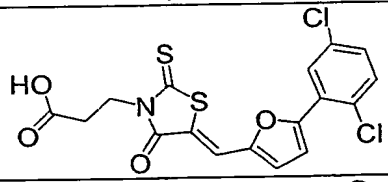
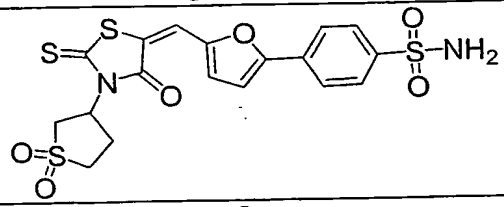
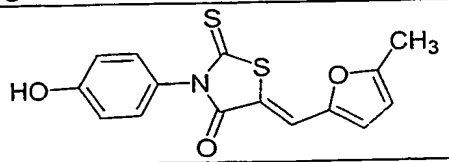
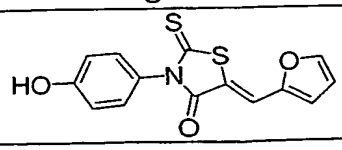
Cpd	Structure	Name
200		3-{5-[(*Z*)-(3-benzyl-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid
201		(5*Z*)-5-[(4-bromo-5-iodo-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
202		(5*E*)-3-(4-fluorophenyl)-5-[(5-methyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
203		(5*E*)-5-[(5-methyl-2-furyl)methylene]-2-thioxo-3-[3-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-one
204		(5*Z*)-3-[4-(diethylamino)phenyl]-5-[(5-methyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
205		(5*Z*)-5-{[5-(2,3-dichlorophenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
206		(5*Z*)-5-{[5-(2-methyl-4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
207		(5*Z*)-5-{[5-(3-methyl-4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

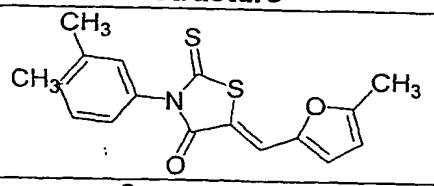
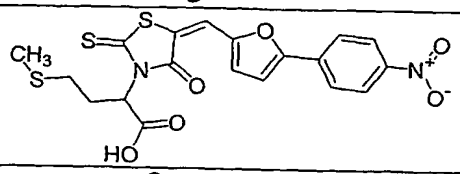
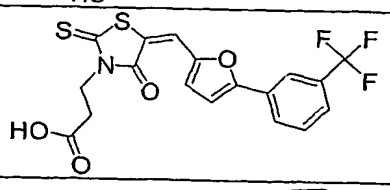
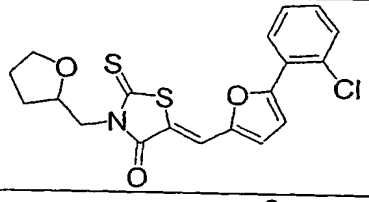
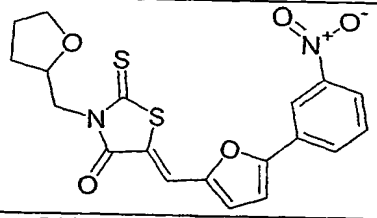
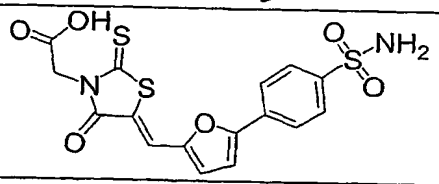
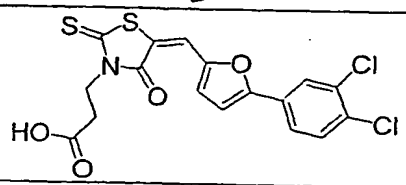
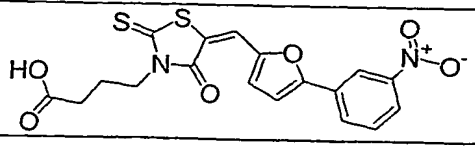
Cpd	Structure	Name
208		{(5Z)-5-[(5-iodo-2-furyl)methylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}acetic acid
209		{(5Z)-5-[(5-bromo-2-furyl)methylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}acetic acid
210		((5Z)-5-{[5-(3-methyl-4-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
211		(5Z)-5-[(5-bromo-2-furyl)methylene]-3-phenyl-2-thioxo-1,3-thiazolidin-4-one
212		(5Z)-3-allyl-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
213		(5Z)-3-allyl-5-[(5-bromo-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
214		(5Z)-3-allyl-5-{[5-(2-methyl-4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
215		(5Z)-3-allyl-5-{[5-(3-methyl-4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

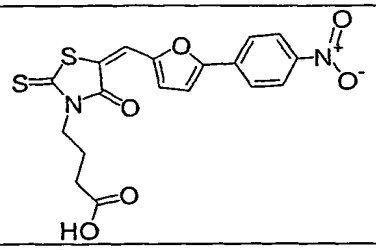
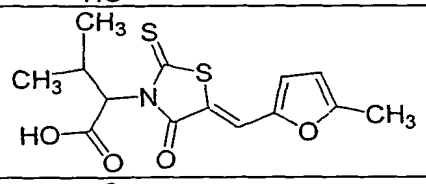
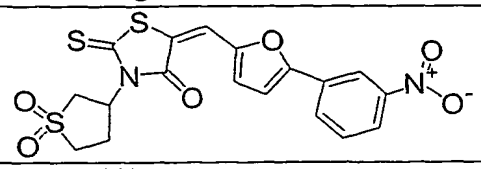
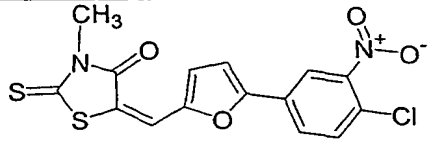
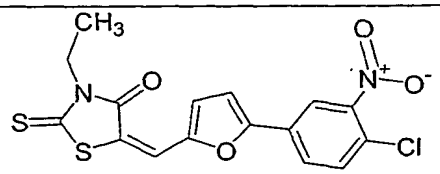
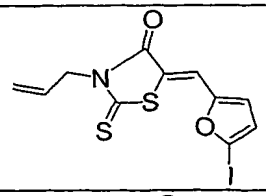
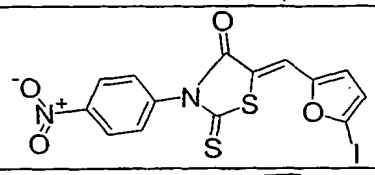
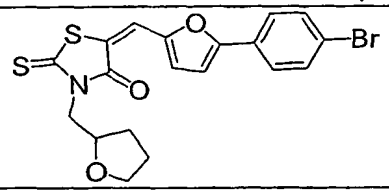
Cpd	Structure	Name
216		(5Z)-3-methyl-5-{[5-(2-methyl-4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
217		(5Z)-3-methyl-5-{[5-(3-methyl-4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
218		(5Z)-3-ethyl-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
219		(5Z)-5-[(5-bromo-2-furyl)methylene]-3-(3-chlorophenyl)-2-thioxo-1,3-thiazolidin-4-one
220		(5Z)-5-[(5-bromo-2-furyl)methylene]-3-(4-methoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one
221		(5Z)-3-benzyl-5-[(5-bromo-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
222		(5Z)-3-benzyl-5-[(5-iodo-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
223		(5Z)-3-cyclohexyl-5-[(5-iodo-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one

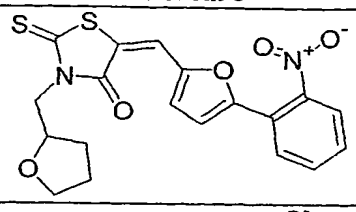
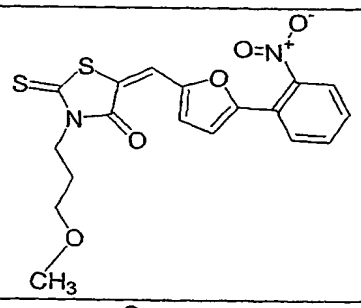
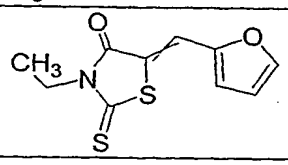
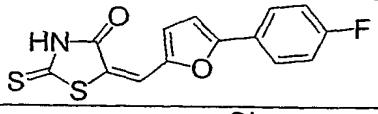
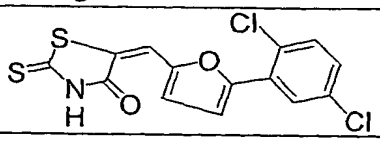
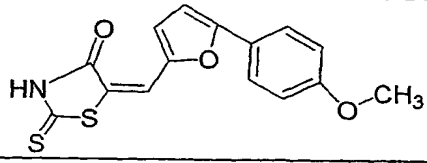
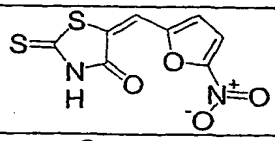
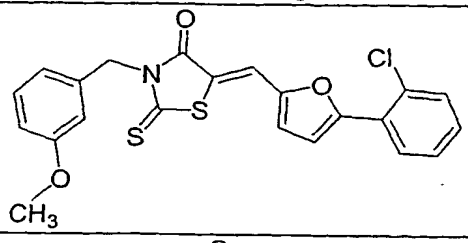
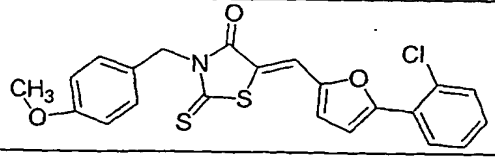
Cpd	Structure	Name
224		6-[(5*E*)-5-(2-furylmethylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]hexanoic acid
225		4-{(5*E*)-5-[(5-methyl-2-furyl)methylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}butanoic acid
226		2-((5*E*)-5-{[5-(2,5-dichlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*,*N*-diethylacetamide
227		(5*E*)-5-[(5-acetyl-2-furyl)methylene]-3-phenyl-2-thioxo-1,3-thiazolidin-4-one
228		(5*Z*)-5-{[5-(3-chlorophenyl)-2-furyl]methylene}-3-(1,1-dioxidotetrahydro-3-thienyl)-2-thioxo-1,3-thiazolidin-4-one
229		((5*Z*)-5-{[5-(3-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetic acid
230		(5*Z*)-5-{[5-(3-chlorophenyl)-2-furyl]methylene}-3-(tetrahydrofuran-2-ylmethyl)-2-thioxo-1,3-thiazolidin-4-one
231		(5*E*)-5-{[5-(3-chlorophenyl)-2-furyl]methylene}-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxo-1,3-thiazolidin-4-one

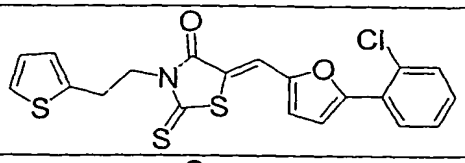
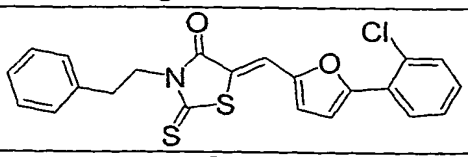
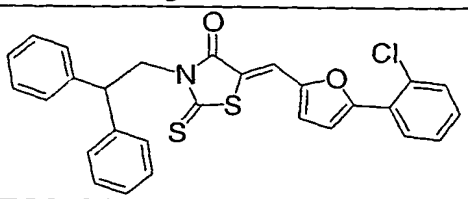
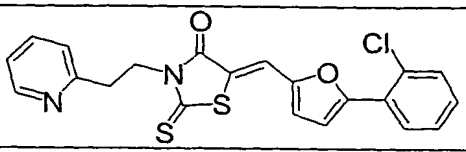
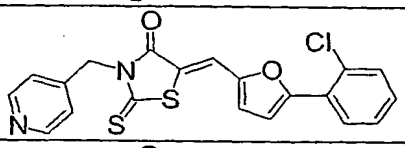
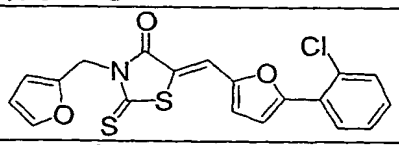
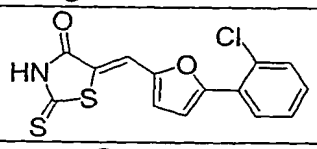
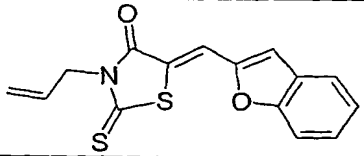
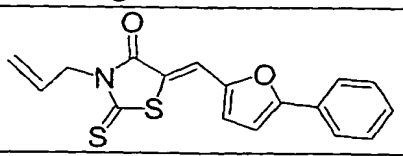
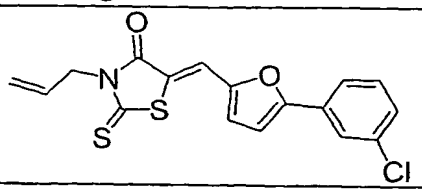
Cpd	Structure	Name
232		(5*E*)-3-[4-(diethylamino)phenyl]-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
233		(5*Z*)-3-(4-ethoxyphenyl)-5-[(5-methyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
234		(5*Z*)-3-(3-methoxyphenyl)-5-[(5-methyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
235		(5*Z*)-3-(2,3-dimethylphenyl)-5-[(5-methyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
236		(5*Z*)-5-(2-furylmethylene)-3-(3-methoxyphenyl)-2-thioxo-1,3-thiazolidin-4-one
237		(5*Z*)-3-(2,3-dimethylphenyl)-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
238		(5*E*)-5-{[5-(4-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
239		(5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
240		(5*E*)-3-(1,1-dioxidotetrahydro-3-thienyl)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

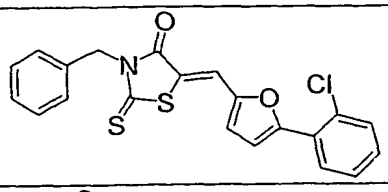
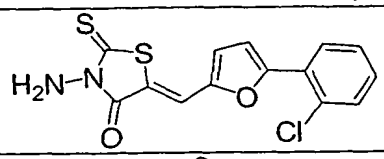
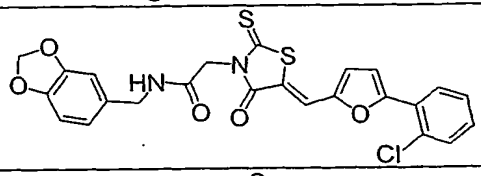
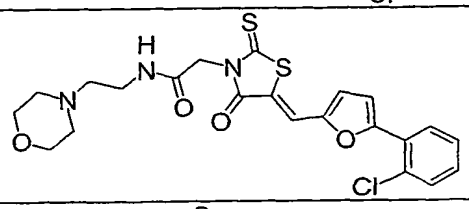
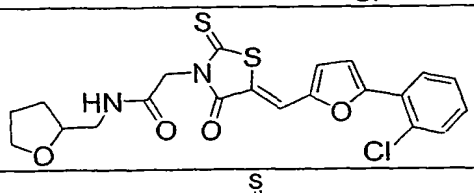
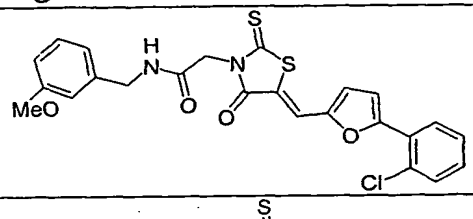
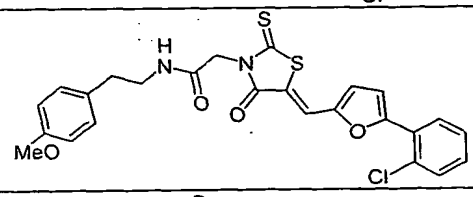
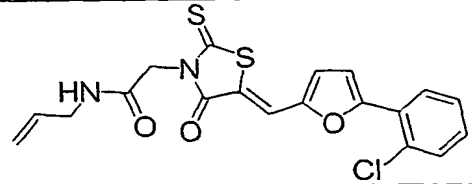
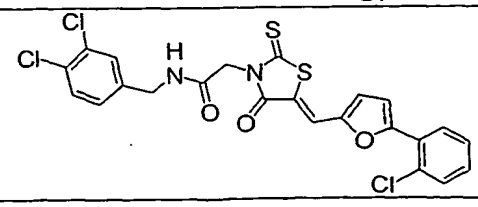
Cpd	Structure	Name
241		3-((5Z)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
242		(5*E*)-5-{[5-(2,5-dichlorophenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
243		(5Z)-5-{[5-(4-methoxy-3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
244		(5Z)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-3-phenyl-2-thioxo-1,3-thiazolidin-4-one
245		(5Z)-5-[(5-iodo-2-furyl)methylene]-3-methyl-2-thioxo-1,3-thiazolidin-4-one
246		3-((5Z)-5-{[5-(2,5-dichlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
247		4-(5-{(*E*)-[3-(1,1-dioxidotetrahydro-3-thienyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)benzenesulfonamide
248		(5Z)-3-(4-hydroxyphenyl)-5-[(5-methyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
249		(5Z)-5-(2-furylmethylene)-3-(4-hydroxyphenyl)-2-thioxo-1,3-thiazolidin-4-one

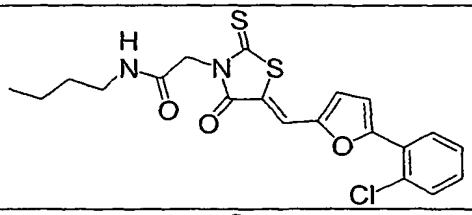
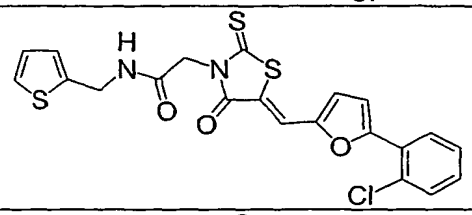
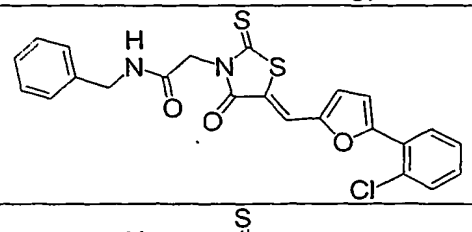
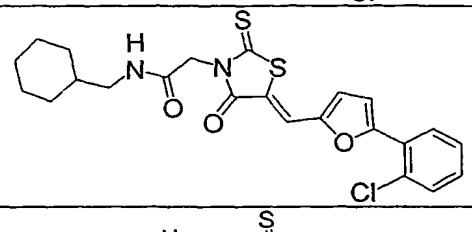
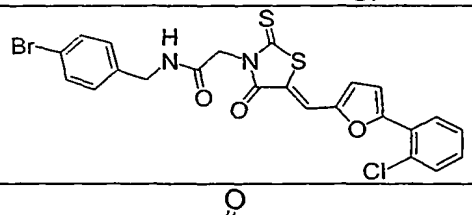
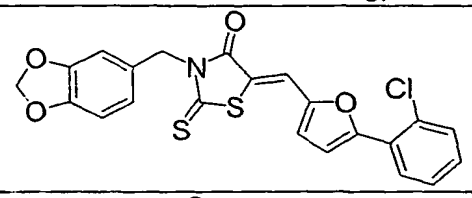
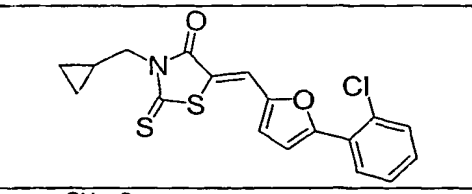
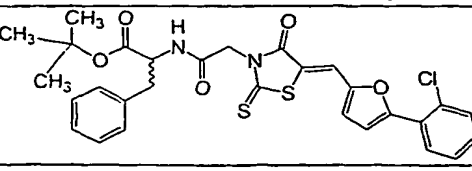
Cpd	Structure	Name
250		(5*Z*)-3-(3,4-dimethylphenyl)-5-[(5-methyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
251		4-(methylthio)-2-((5*E*)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)butanoic acid
252		3-[(5*E*)-4-oxo-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-3-yl]propanoic acid
253		(5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(tetrahydrofuran-2-ylmethyl)-2-thioxo-1,3-thiazolidin-4-one
254		(5*Z*)-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-3-(tetrahydrofuran-2-ylmethyl)-2-thioxo-1,3-thiazolidin-4-one
255		[(5*Z*)-5-({5-[4-(aminosulfonyl)phenyl]-2-furyl}methylene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]acetic acid
256		3-((5*E*)-5-{[5-(3,4-dichlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)propanoic acid
257		4-((5*E*)-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)butanoic acid

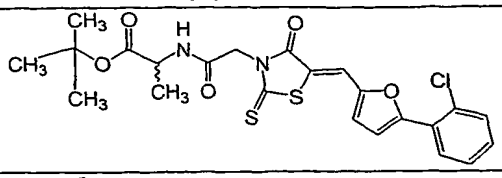
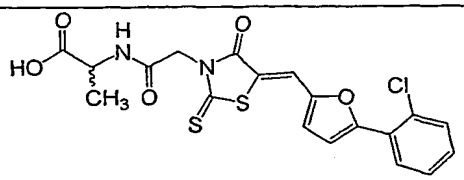
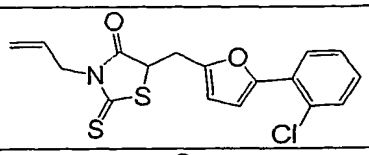
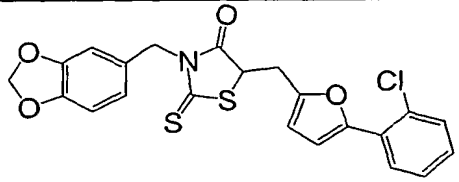
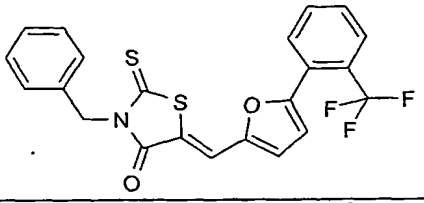
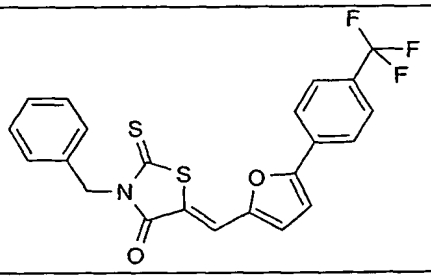
Cpd	Structure	Name
258		4-((5*E*)-5-{[5-(4-nitrophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)butanoic acid
259		3-methyl-2-{(5*Z*)-5-[(5-methyl-2-furyl)methylene]-4-oxo-2-thioxo-1,3-thiazolidin-3-yl}butanoic acid
260		(5*E*)-3-(1,1-dioxidotetrahydro-3-thienyl)-5-{[5-(3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
261		(5*E*)-5-{[5-(4-chloro-3-nitrophenyl)-2-furyl]methylene}-3-methyl-2-thioxo-1,3-thiazolidin-4-one
262		(5*E*)-5-{[5-(4-chloro-3-nitrophenyl)-2-furyl]methylene}-3-ethyl-2-thioxo-1,3-thiazolidin-4-one
263		(5*Z*)-3-allyl-5-[(5-iodo-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
264		(5*Z*)-5-[(5-iodo-2-furyl)methylene]-3-(4-nitrophenyl)-2-thioxo-1,3-thiazolidin-4-one
265		(5*E*)-5-{[5-(4-bromophenyl)-2-furyl]methylene}-3-(tetrahydrofuran-2-ylmethyl)-2-thioxo-1,3-thiazolidin-4-one

Cpd	Structure	Name
266		(5*E*)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-3-(tetrahydrofuran-2-ylmethyl)-2-thioxo-1,3-thiazolidin-4-one
267		(5*E*)-3-(3-methoxypropyl)-5-{[5-(2-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
268		(5*Z*)-3-ethyl-5-(2-furylmethylene)-2-thioxo-1,3-thiazolidin-4-one
269		(5*E*)-5-{[5-(4-fluorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
270		(5*E*)-5-{[5-(2,5-dichlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
271		(5*E*)-5-{[5-(4-methoxyphenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
272		(5*E*)-5-[(5-nitro-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
273		(5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(3-methoxybenzyl)-2-thioxo-1,3-thiazolidin-4-one
274		(5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(4-methoxybenzyl)-2-thioxo-1,3-thiazolidin-4-one

Cpd	Structure	Name
275		(5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-[2-(2-thienyl)ethyl]-2-thioxo-1,3-thiazolidin-4-one
276		(5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(2-phenylethyl)-2-thioxo-1,3-thiazolidin-4-one
277		(5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(2,2-diphenylethyl)-2-thioxo-1,3-thiazolidin-4-one
278		(5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(2-pyridin-2-ylethyl)-2-thioxo-1,3-thiazolidin-4-one
279		(5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(pyridin-4-ylmethyl)-2-thioxo-1,3-thiazolidin-4-one
280		(5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(2-furylmethyl)-2-thioxo-1,3-thiazolidin-4-one
281		(5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
282		(5Z)-3-allyl-5-(1-benzofuran-2-ylmethylene)-2-thioxo-1,3-thiazolidin-4-one
283		(5Z)-3-allyl-5-[(5-phenyl-2-furyl)methylene]-2-thioxo-1,3-thiazolidin-4-one
284		(5Z)-3-allyl-5-{[5-(3-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

Cpd	Structure	Name
285		(5Z)-3-benzyl-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
286		(5Z)-3-amino-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
287		*N*-(1,3-benzodioxol-5-ylmethyl)-2-((5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide
288		2-((5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*-(2-morpholin-4-ylethyl)acetamide
289		2-((5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*-(tetrahydrofuran-2-ylmethyl)acetamide
290		2-((5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*-(3-methoxybenzyl)acetamide
291		2-((5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*-[2-(4-methoxyphenyl)ethyl]acetamide
292		*N*-allyl-2-((5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide
293		2-((5Z)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*-(3,4-dichlorobenzyl)acetamide

Cpd	Structure	Name
294		*N*-butyl-2-((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide
295		2-((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*-(2-thienylmethyl)acetamide
296		*N*-benzyl-2-((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide
297		2-((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)-*N*-(cyclohexylmethyl)acetamide
298		*N*-(4-bromobenzyl)-2-((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetamide
299		(5*Z*)-3-(1,3-benzodioxol-5-ylmethyl)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
300		(5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-3-(cyclopropylmethyl)-2-thioxo-1,3-thiazolidin-4-one
301		*tert*-butyl *N*-[((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetyl]phenylalaninate

Cpd	Structure	Name
302		*tert*-butyl *N*-[((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetyl]alaninate
303		*N*-[((5*Z*)-5-{[5-(2-chlorophenyl)-2-furyl]methylene}-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)acetyl]alanine
304		3-allyl-5-{[5-(2-chlorophenyl)-2-furyl]methyl}-2-thioxo-1,3-thiazolidin-4-one
305		3-(1,3-benzodioxol-5-ylmethyl)-5-{[5-(2-chlorophenyl)-2-furyl]methyl}-2-thioxo-1,3-thiazolidin-4-one
306		(5Z)-3-benzyl-5-{[5-(2-trifluoromethylphenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one
307		(5Z)-3-benzyl-5-{[5-(4-trifluoromethylphenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

[0027] While particular geometric isomers (*i.e.*, E or Z) are displayed throughout this specification, the invention also comprises the E or Z geometric isomers and mixtures thereof of all of the compounds of paragraphs [0016] - [0020], as well as the compounds disclosed in the table in paragraph [0026]. The E and Z geometric isomers can be interconverted by photolysis, photo irradiation or exposure to free radicals. *See, e.g.*, Ishida *et al.*, *Tetrahedron Lett.* **30**, 959 (1989). Exposure to certain solvents, *e.g.*, DMSO, will facilitate conversion of an E isomer to the Z form.

[0028] The compounds in the table above can be prepared using art recognized methods. All of the compounds in this application were named using ChemDraw Ultra version 6.0.2, which is

available through Cambridgesoft.com, 100 Cambridge Park Drive, Cambridge, MA 02140, Namepro version 5.09, which is available from ACD labs, 90 Adelaide Street West, Toronto, Ontario, M5H, 3V9, Canada, or were derived therefrom.

[0029] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (e.g. CH_3CH_2-), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (e.g.,-CH_2CH_2-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (i.e., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as (A)a B , wherein a is 0 or 1. In such instances, when a is 0 the moiety is B and when a is 1 the moiety is A B . Also, a number of moieties disclosed herein exist in multiple tautomeric forms, all of which are intended to be encompassed by any given tautomeric structure. Other stereochemical forms of the compounds of the invention are also encompassed including but not limited to enantiomers, diastereomers, and other isomers such as rotamers.

[0030] For simplicity, when a substituent can be of a particular chemical class differing by the number of atoms or groups of the same kind in the moiety (e.g., alky, which can be C_1, C_2, C_3, etc.), the number of repeated atoms or groups is represented by a range (e.g., C_1-C_6 alkyl). In such instances each and every number in that range and all sub ranges are specifically contemplated. Thus, C_1-C_3 alkyl means C_1, C_2 , C_3 , C_{1-2}, C_{1-3} , and C_{2-3} alkyl.

[0031] In addition to individual preferred embodiments of each substituent defined herein, the invention also comprises all combinations of preferred substituents.

[0032] The term "alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1 to 30 carbon atoms, preferably 1 to 15 carbon atoms, more preferably 1 to 6 carbon atoms, which is optionally substituted with one, two or three substituents. Unless otherwise specified, the alkyl group may be saturated, unsaturated, or partially unsaturated. As used herein, therefore, the term "alkyl" is specifically intended to include alkenyl and alkynyl groups, as well as

saturated alkyl groups, unless expressly stated otherwise. Preferred alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, tert butyl, isobutyl, pentyl, hexyl, vinyl, allyl, isobutenyl, ethynyl, and propynyl.

[0033] As employed herein, a "substituted" alkyl, cycloalkyl, aryl, or heterocyclic group is one having between one and about four, preferably between one and about three, more preferably one or two, non hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, nitro, haloalkyl, alkyl, alkaryl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, alkoxycarbonyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups.

[0034] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12, preferably 3 to 8 carbons, wherein the cycloalkyl group additionally is optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cycloоctyl.

[0035] The term "hydrocarbyl" as employed herein includes all alkyl moieties and all cycloalkyl moieties (both as defined above), each alone or in combination. Thus, for example, hydrocarbyl includes methyl, ethyl, propyl, n-butyl, isobutyl, cyclopropyl, cyclohexyl, cyclopropyl-CH_2 , cyclohexyl-$(CH_2)_3$, etc.

[0036] An "aryl" group is a C_6-C_{14} aromatic moiety comprising one to three aromatic rings, which is optionally substituted. Preferably, the aryl group is a C_6-C_{10} aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is C_1-C_6 alkyl (C_6-C_{10})aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl. An "alkaryl" or "alkylaryl" group is an aryl group having one or more alkyl substituents. Examples of alkaryl groups include, without limitation, tolyl, xylyl, mesityl, ethylphenyl, tert butylphenyl, and methylnaphthyl.

[0037] A "heterocyclic" group (or "heterocyclyl) is a non-aromatic mono-, bi-, or tricyclic structure having from about 3 to about 14 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S. One ring of a bicyclic heterocycle or two rings of a tricyclic heterocycle may be aromatic, as in indan and 9,10-dihydro anthracene. The heterocyclic group is optionally

substituted on carbon with oxo or with one of the substituents listed above. The heterocyclic group may also independently be substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino.

[0038] In certain preferred embodiments, the heterocyclic group is a heteroaryl group. As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 pi electrons shared in a cyclic array; and having, in addition to carbon atoms, between one and about three heteroatoms selected from the group consisting of N, O, and S. Preferred heteroaryl groups include, without limitation, thienyl, benzothienyl, furyl, benzofuryl, dibenzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, quinoxalinyl, tetrazolyl, oxazolyl, thiazolyl, and isoxazolyl.

[0039] In certain other preferred embodiments, the heterocyclic group is fused to an aryl or heteroaryl group. Examples of such fused heterocycles include, without limitation, tetrahydroquinolinyl and dihydrobenzofuranyl. Additional preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzodioxolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3 b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isothiazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazolidinyl, pyrazolinyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, quinazolinyl, 4H-quinolizinyl, quinuclidinyl, tetrahydroisoquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0040] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non limiting example, substituted phenyls include 2-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 2-fluoro-3-propylphenyl. As another non limiting example, substituted n octyls include 2,4-dimethyl-5-ethyloctyl and 3-cyclopentyloctyl. Included within this definition are methylenes (-CH_2-) substituted with oxygen to form carbonyl (-CO).

[0041] Unless otherwise stated, as employed herein, when a moiety (e.g., cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (e.g., an annular -CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, , alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

(a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino,

(b) C_1-C_5 alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, C_2-C_8 acyl, C_2-C_8 acylamino, C_1-C_8 alkylthio, arylalkylthio, arylthio, C_1-C_8 alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C_0-C_6 N-alkyl carbamoyl, C_2-C_{15} N,N-dialkylcarbamoyl, C_3-C_7 cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C_3-C_7 heterocycle, or any of these rings fused or spiro fused to a cycloalkyl, heterocyclyl, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; and

(c) -$(CH_2)_s$ $NR_{30}R_{31}$, wherein s is from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6, and R_{30} and R_{31} are each independently hydrogen, cyano, oxo, carboxamido, amidino, C_1-C_8 hydroxyalkyl, C_1-C_3 alkylaryl, aryl C_1-C_3 alkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, aryl C_1-C_3 alkoxycarbonyl, C_2-C_8 acyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, aroyl,

aryl, cycloalkyl, heterocyclyl, or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or

R_{30} and R_{31} taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents from (a), above.

[0042] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, and iodine.

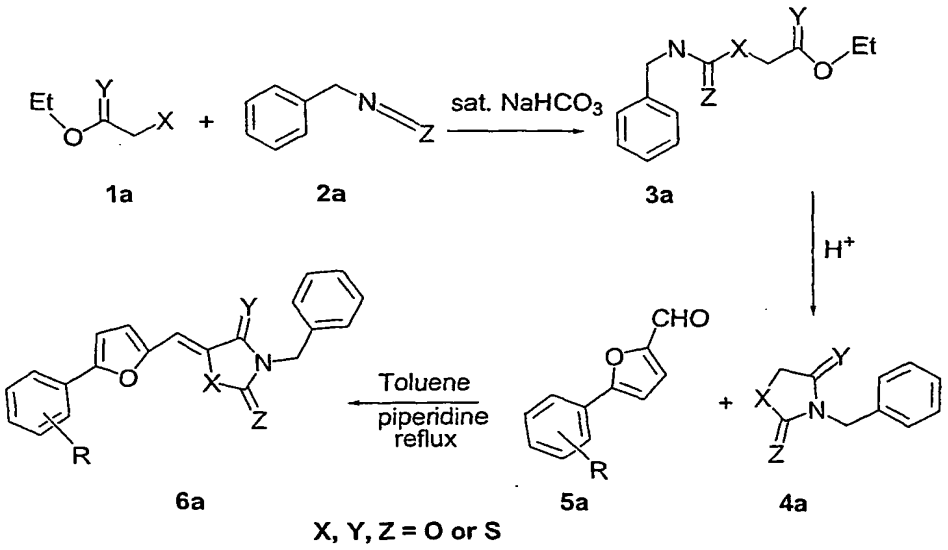
[0043] As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent.

[0044] The term "acylamino" refers to an amide group attached at the nitrogen atom. The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom. The nitrogen atom of an acylamino or carbamoyl substituent may be additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. The term "amino" is meant to include NH_2, alkylamino, arylamino, and cyclic amino groups.

GENERAL SYNTHETIC PROCEDURE

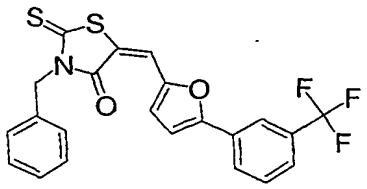
[0045] The compounds of the invention can be prepared using general synthetic procedures. The starting components are readily prepared from carboxylic acids, aldehydes, alkyls, benzene and phenol to a variety of substitutions can be made according to procedures well known to those skilled in the art and commercially available.

Scheme 1



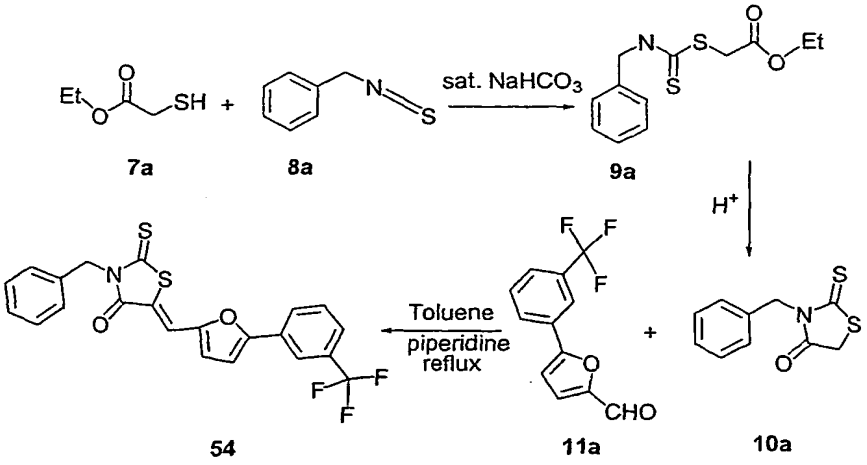
[0046] The compounds of the invention can be prepared according to Scheme 1. Scheme 1 illustrates only one way to prepare the compounds of the invention and is not meant to be limiting in any way. One skilled in the art would recognize that to obtain the compounds of the invention, reactant compounds **2a** and **5a** can be replaced with suitable compounds that have a variety of substituents in the phenyl and furanyl portions. The example below serves to illustrate this point.

Example 1



(5*E*)-3-benzyl-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one

Scheme II



Step 1. Synthesis of benzyl rhodanine (10a)

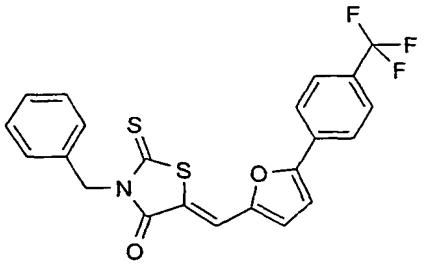
[0047] To a mixture of 10 mmol (1.1 mL; 1.2 g) of ethylthio glycolate (**7a**) and 11 mmole (1.64 g) of benzyl isothiocyanate (**8a**) was added 26 mL of saturated aqueous sodium bicarbonate. The reaction mixture was stirred at 40°C for 3 hrs. About 5 mL of methanol was added to enhance solubility. The LC/MS analysis indicated two peaks: the major (85%) corresponded to the desired rhodanine (**10a**) and the minor peak was that of the uncyclized adduct (**9a**). The reaction mixture was treated with water and neutralized by addition of acetic acid. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were concentrated to a volume of 10 mL, and 2 mL of acetic acid was added to this. The resulting mixture was heated at 50°C overnight. Analysis by TLC showed one spot. The product was further purified by column chromatography using silica-gel and

35% ethyl acetate:hexane mixture as the mobile phase. The fractions corresponding to compound **10a** were combined to give 2.18 g of pale reddish-yellow needles (yield = 98%). ^{1}H NMR ($CDCl_3$) □ 3.972 (s, 2H); 5.180 (s, 2H); 7.28 (m, 3H); 7.405 (m, 2H). MS (ES^-); 222.03 (M-1).

Step 2. Synthesis of Title Compound

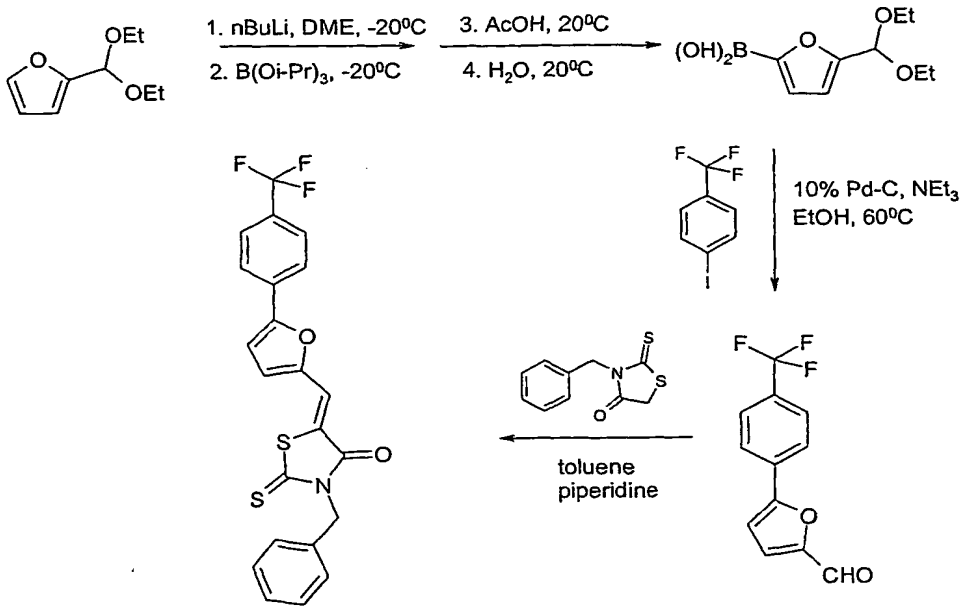
[0048] To 1.52 g (0.65 mmole) of benzyl rhodanine (**10a**) was added 30 mL of toluene, 1.56 g (0.65 mmole) of 5-(3-trifluoromethylphenyl)furan-2-carboxaldehyde (**11a**), and 0.8 mL of piperidine. The mixture was heated under reflux for 4 hours, and the reaction was monitored by TLC. At the end of the 4 hours, the TLC analysis showed no trace of the starting materials. The reaction mixture was allowed to cool and a bright yellow solid formed which was filtered and washed with hexane. The product was further purified by column chromatography using silica-gel and 40% ethyl acetate:hexane mixture as the mobile phase. Yield was 2.6 g (86%). ^{1}H NMR : ($CDCl_3$) □ 5.335 (s, 2 H); 6.928-6.961 (dd, 2H, J=3.4 Hz); 7.265-7.35 (m, 3H); 7.449-7.488 (m, 3H); 7.613-7.633 (m, 2H); 7.934 (br.s, 1H); 9.945-8.15 (m, 1H). MS; ES^+ 446.21 (M+1).

Example 2



(5Z)-3-benzyl-5-{[5-(4-trifluoromethylphenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

Scheme III



1. 5-(Diethoxymethyl)-2-furylboronic acid

[0049] To a solution of 2-(diethoxymethyl) furan 16.9 ml 100 mmol) in 150 ml of DME at –20°C, was added 120 mmol of n-BuLi in hexanes dropwise so that the temperature remains below–15°C. The reaction is stirred for a further two hours at –20°C. Triisopropylborate(22.7 ml, 120m.mol) was then added. The reaction mixture was then allowed to warm up to room temperature. 7.5mL of acetic acid was then added to the reaction mixture followed by addition of 10ml of water. The solution was used directly in the next step.

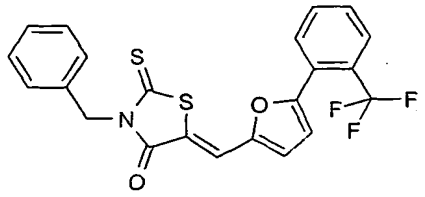
2. 5-[4-(Trifluromethyl) phenyl]- 2-furaldehyde

[0050] To (20 ml, 5 mmol) of the crude boronic acid solution was added (544 mg, 2 mmol) of 4-iodo benzotrifluoride followed by addition of 7 ml of ethanol, 0.6 ml of triethylamine and 54 mg of 10%Pd/C. The reaction mixture was stirred at 60°C until it was complete by HPLC. The reaction mixture was cooled and filteredand washed with DME till filtrate was colorless. The filtrate was treated with 10 ml of water and 0.8 ml of trifluoroacetic acid and stirred to remove the acetal group. The resulting solution was washed with brine and saturated sodium bicarbonate solutions. The organic layer was dried and solvent evaporated to yield the crude product which was purified by column chromatography using ethyl acetate: hexane 1:4 mixture. The appropriate fractions were combined and evaporated to yield 378 mg of the product 78% yield.

3. (5Z)-3-benzyl-5-{[5-(4-trifluoromethylphenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

[0051] To 44.6 mg of benzylrhodanine was added 48 mg of 5-[4-(Trifluromethyl) phenyl]- 2-furaldehyde and 10 ml of toluene and 0.1 ml of piperidine. The mixture was refluxed for four hours when an examination of TLC indicated that starting material had been consumed. The reaction mixture was cooled, the solid formed was filtered and washed several times with hexane and dried to yield 82 mg 91% of pure product.

Example 3



(5Z)-3-benzyl-5-{[5-(2-trifluoromethylphenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

[0052] To 44.6mg (0.2 mmol) of benzyl rhodanine was added 48 mg (0.2 mmol) of 5-[2-(trifluoromethyl)phenyl]-2-furaldehyde and 10 mL of toluene. 0.1 ml of piperidine was added to this mixture and the reaction mixture refluxed for four hours. Examination of TLC at this time showed that the reaction was complete. The reaction mixture was cooled. The solid formed was filtered off and the washed several times with hexane. The reaction yielded 80.1 mg (90%) yield of R911572. ^{1}H NMR : ($CDCl_3$) δ 5.324 (s, 2H); 6.945 (br.s, 2H) ; 7.345-7.268 (m,3H); 7.547-7.438 (m,4H); 7.675-7.726 (t, 1H, J=7.5Hz); 7.781-7.7807 (d, 1H , J= 7.8 Hz); 7.926-7.900 (d, 1H, J= 7.8 Hz). MS; ES^+ 445.95 (M+1)

PHARMACEUTICAL COMPOSITIONS

[0053] In a second aspect, the invention provides pharmaceutical compositions comprising an inhibitor of ubiquitination according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Suitable excipients are described in "Handbook of Pharmaceutical Excipients," 4th Edition, Rowe, R. C., Sheskey, P.J., and Weller, P.J., editors, American Pharmaceutical Association, Chicago, IL (2003), which is incorporated by reference in its entirety. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration to the patient by any route, including, without limitation, parenteral, oral, sublingual, subcutaneous, intravenous, intraperitoneal, intramuscular, intrapulmonary, vaginal, rectal, intraocular, transdermal, topical, intranasal, intratracheal, or intrarectal. In some instances, the compounds of

the invention are administered directly as a solution or spray. In certain preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0054] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, pharmaceutical compositions according to the invention may contain, in addition to the inhibitor, carrier proteins (for example, such as serum albumin), diluents, fillers (for example microcrystalline cellulose, lactose, corn and other starches), binding agents, sweeteners and flavoring agents, coloring agents, polyethylene glycol, salts, buffers, stabilizers, solubilizers, flavors, dyes and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in many well known references to one skilled in the art, for example, Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, PA, 1990.

[0055] As used herein, the term pharmaceutically acceptable salts refers to salts and complexes that retain the desired biological activity of the compounds of the invention and exhibit minimal or no undesired toxicological effects. Pharmaceutically acceptable salts include both the acid and base addition salts. Examples of acid salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, fumaric acid, tartaric acid, citric acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid and the like. Examples of base salts include those derived from inorganic bases such as potassuim, sodium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum and the like. Salts from derived from suitable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines, cyclic amines, and basic ion exchange resins such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine and ethanolamine.

[0056] The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the

formula -NR^+ Z^-, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate). Moreover, the compounds of the invention can also be administered as prodrugs which can be converted to the active form in vivo.

[0057] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. The compounds can be formulated in a variety of ways depending on the manner of administration. The concentration of the active compounds in these formulations can vary from 0.1 to 100% wt/wt. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 550 mg/kg, preferably 300 to 550 mg/kg, more preferably 0.1 to 100 mg/kg per day, and more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[0058] When administered systemically, the ubiquitination inhibitor is preferably administered at a sufficient dosage to attain a blood level of the inhibitor from about 0.01 μM to about 100 μM, more preferably from about 0.05 μM to about 50 μM, still more preferably from about 0.1 μM to about 25 μM, and still yet more preferably from about 0.5 μM to about 20 μM. For localized administration, much lower concentrations than this may be effective, and much higher concentrations may be tolerated. One of skill in the art will appreciate that the dosage of ubiquitination inhibitor necessary to produce a therapeutic effect may vary considerably depending on the tissue, organ, or the particular animal or patient to be treated.

[0059] By "administration" is meant administering a therapeutically effective dose to a cell or patient. A therapeutically effective dose is a dose that produces the effects for which it is administered. The exact dose depends on the purpose of the treatment and can be ascertained by one skilled in the art using known techniques.

[0060] By "patient" is meant a human or other animal and organisms, for example, experimental animals. Thus, the compounds can be used for both human therapy and veterinary applications. In a preferred embodiment, the patient is human.

Inhibition of Ubiquitination

[0061] In a third aspect, the invention provides a method of inhibiting ubiquitination in a cell, comprising contacting a cell in which inhibition of ubiquitination is desired with an inhibitor of ubiquitination of the invention.

[0062] Measurement of the ubiquitination can be achieved using known methodologies. (See, for example, WO 01/75145, US-2002-0042083-A1 and WO 03/076608, each of which is incorporated by reference in its entirety.)

[0063] Preferably, the method according to the third aspect of the invention causes an inhibition of cell proliferation of contacted cells. The phrase "inhibiting cell proliferation" is used to denote an ability of an inhibitor of ubiquitination to retard the growth of cells contacted with the inhibitor as compared to cells not contacted. An assessment of cell proliferation can be made by counting contacted and non-contacted cells using a Coulter Cell Counter (Coulter, Miami, FL), photographic analysis with Array Scan II (Cellomics) or a hemacytometer. Where the cells are in a solid growth (e.g., a solid tumor or organ), such an assessment of cell proliferation can be made by measuring the growth with calipers and comparing the size of the growth of contacted cells with non-contacted cells.

[0064] Preferably, growth of cells contacted with the inhibitor is retarded by at least 50% as compared to growth of non-contacted cells. More preferably, cell proliferation is inhibited by 100% (*i.e.*, the contacted cells do not increase in number). Most preferably, the phrase "inhibiting cell proliferation" includes a reduction in the number or size of contacted cells, as compared to non-contacted cells. Thus, an inhibitor of ubiquitination according to the invention that inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (*i.e.*, to apoptose), or to undergo necrotic cell death.

[0065] In some preferred embodiments, the contacted cell is a neoplastic cell. The term "neoplastic cell" is used to denote a cell that shows aberrant cell growth. Preferably, the aberrant cell growth of a neoplastic cell is increased cell growth. A neoplastic cell may be a hyperplastic cell, a

cell that shows a lack of contact inhibition of growth in vitro, a benign tumor cell that is incapable of metastasis in vivo, or a cancer cell that is capable of metastasis in vivo and that may recur after attempted removal. The term "tumorigenesis" is used to denote the induction of cell proliferation that leads to the development of a neoplastic growth. In some embodiments, the ubiquitination inhibitor induces cell differentiation in the contacted cell. Thus, a neoplastic cell, when contacted with an inhibitor of ubiquitination may be induced to differentiate, resulting in the production of a non-neoplastic daughter cell that is phylogenetically more advanced than the contacted cell.

Treatment for Cell Proliferative Diseases or Conditions

[0066] In some preferred embodiments, the contacted cell is in an animal. Thus, in a fourth aspect the invention provides a method for treating a cell proliferative disease or condition in an animal, comprising administering to an animal in need thereof an effective amount of an inhibitor of ubiquitination of the invention. Preferably, the animal is a mammal, more preferably a domesticated mammal. Most preferably, the animal is a human.

[0067] The term "cell proliferative disease or condition" is meant to refer to any condition characterized by aberrant cell growth, preferably abnormally increased cellular proliferation. Examples of such cell proliferative diseases or conditions include, but are not limited to, cancer, restenosis, and psoriasis. In particularly preferred embodiments, the invention provides a method for inhibiting neoplastic cell proliferation in an animal comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of a ubiquitination inhibitor of the invention. Most preferably, the invention provides a method for treating cancer comprising administering to a patient in need thereof an effective amount of an inhibitor of ubiquitination of the invention.

[0068] The term "therapeutically effective amount" is meant to denote a dosage sufficient to cause inhibition of ubiquitination in the cells of the subject, or a dosage sufficient to inhibit cell proliferation or to induce cell differentiation in the subject. Administration may be by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain particularly preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0069] When administered systemically, the ubiquitination inhibitor is preferably administered at a sufficient dosage to attain a blood level of the inhibitor from about 0.01 μM to about 100 μM, more preferably from about 0.05 μM to about 50 μM, still more preferably from about 0.1 μM to about 25 μM, and still yet more preferably from about 0.5 μM to about 20 μM. For localized administration, much lower concentrations than this may be effective, and much higher concentrations may be tolerated. One of skill in the art will appreciate that the dosage of ubiquitination inhibitor necessary to produce a therapeutic effect may vary considerably depending on the tissue, organ, or the particular animal or patient to be treated.

BIOLOGICAL ASSAY

[0070] The ubiquitination inhibition properties of compounds of the invention can be assayed by suitable methods that measure ubiquitin ligase activities. For example, methods that measure the ubiquitin ligase activities of MDM2 or APC2/APC11 can be used to assay the compounds of the invention.

Assay Example 1

MDM2 ASSAY

[0071] The MDM2 assay used for measuring the attachment of ubiquitin to p53 was carried out as described in WO 01/75145 and WO 03/076608, each of which is incorporated by reference in its entirety. Briefly, Flag-ubiquitin was added to a solution containing GST-MDM2, E1, E2 and His-p53 and the reaction was carried out at 37°C for 1 hr. After completion of the reaction, a sample of the solution was resolved by SDS-PAGE, analyzed by Western blot and the ligation of ubiquitin to p53 was measured by immunodetection of the ubiquitin-p53 complex using mouse anti-Flag and anti-mouse Ig-HRP.

[0072] The MDM2 assay was also carried out in Nickel-substrate 96-well plates using His-tagged p53. In this method, Flag-ubiquitin was added to a solution containing MDM2, E1, E2 and His-p53 and the reaction was carried out at room temperature for 1 hr. After the reaction was completed, the wells were washed with PBS and to each well was added mouse anti-Flag and anti-mouse Ig-HRP. The plates were then incubated for 1 hour and then washed again with PBS to remove excess antibodies. Luminol was then added to each well and the ligation of ubiquitin to p53 was measured by luminescence to detect the ubiquitin-p53 complex.The compounds to be assayed were dissolved in DMSO and added before the addition of Flag-ubiquitin. Activity in the presence of the compound was determined relative to a parallel control in which only DMSO was added. Values of the IC50 were

typically determined using different concentrations of the compound, although as few as 2 concentrations may be used to approximate the IC50 value.

Assay Example 2

APC-11/APC-2 Ligase Assay

[0073] E3 (His-APC11/APC2 – "APC") auto-ubiquitination was measured as described in US Patent Application No. 09/826,312 (Publication No. US-2002-0042083-A1), which is incorporated by reference in its entirety. Details of the protocol are described below. Activity in the presence of the compound was determined relative to a parallel control in which only DMSO was added. Values of the IC_{50} were typically determined using 6 or 8 different concentrations of the compound, although as few as 2 concentrations may be used to approximate the IC_{50} value.

[0074] Nickel-coated 96-well plates (Pierce 15242) were blocked for 1 hour with 100 µl of blocking buffer at room temperature. The plates were washed 4 times with 225 µl of 1×PBS and 80 µl of the reaction buffer were added that contained 100 ng/well of Flag-ubiquitin. To this, 10 µl of the test compound diluted in DMSO were added. After the test compound was added, 10 µl of E1 (human), E2 (Ubch5c), and APC in Protein Buffer was added to obtain a final concentration of 5 ng/well of E1, 20 ng/well of E2 and 100 ng/well of APC. The plates were shaken for 10 minutes and incubated at room temperature for 1 hour. After incubation, the plates were washed 4 times with 225µl of 1×PBS and 100 µl/well of Antibody Mix were added to each well. The plates were incubated at room temperature for another hour after which they were washed 4 times with 225 µl of 1xPBS and 100 µl/well of Lumino substrate were added to each well. The luminescence was measured by using a BMG luminescence microplate reader.

[0075] To prepare the Blocking Buffer (1 liter; 1% Casein in 1×PBS), 10 grams of Casein (Hammersten Grade Casein from Gallard-Schlesinger Inc. #440203) were placed into 1 liter of 1×PBS, stirred on a hot plate and kept between 50-60°C for an hour. The buffer was allowed to cool to room temperature and then filtered using a Buchner Funnel (Buchner filter funnel 83 mm 30310-109) and Whatman filter paper (Whatman Grade No.1 Filter paper 28450-070). It was stored at 4°C until used.

[0076] The reaction buffer consisted of 62.5 mM Tris pH 7.6 (Trizma Base – Sigma T-8524), 3 mM $MgCl_2$ (Magnesium Chloride – Sigma M-2393), 1 mM DTT (Sigma D-9779), 2.5 mM ATP (Roche

Boehringer Mann Corp. 635-316), 100 ng/well of Flag-ubiquitin, 0.1% BSA (Sigma A-7906), and 0.05% Tween-20 (Sigma P-7949).

[0077] The Protein Buffer consisted of 20 mM Tris pH 7.6, 10% glycerol (Sigma G-5516) and 1 mM DTT.

[0078] The antibody mix consisted of 0.25% BSA (Sigma A-7906) in 1X PBS, 1/50,000 anti-Flag (Sigma F-3165), 1/100,000 of anti-Mouse IgG-HRP (Jackson Immunoresearch #115-035-146).

[0079] The substrate mix consisted of SuperSignal Substrate from Pierce (catalog number 37070ZZ) and was prepared by mixing 100 ml of the peroxide solution, 100 ml of the enhancer solution and 100 ml of Milli-Q® water.

[0080] A second ubiquitin assay was performed substantially as described above, with a few modifications. No nickel substrate was used in the reaction wells, so all of the components were free in solution. Equal amounts of fluorescein labeled ubiquitin moiety and labeled ubiquitin moiety were used. The reaction was performed at room temperature for 2 hours in a volume of 100-150 µl, then stopped with 50 µl of 0. 5M EDTA, pH 8.

[0081] Following the reaction, the products were separated in PBS with 1 mM TCEP by HPLC on a Superdex-75 HR 10/30 size-exclusion column using fluorescence emission detection. A larger molecular weight cutoff gel-filtration column (*e.g.*, Superdex 200 HR 10/30) could be used to resolve individual ligation species.

[0082] Table 1 below lists representative IC_{50} values of the compounds of the invention determined by the assays described above. Whereas each compound recited in the table below was presented above as a specific geometric isomer (*i.e.*, 5E or 5Z), it is expected that the compounds tested to generate the data in the table below were a mixture of the 5E and 5Z geometric isomers.

Cpd	LIGASE E3 APC2/APC11 H E1	LIGASE E3 APC2/APC11 H E1/GEL	LIGASE_E3 MDM2/P53
1	2, 4	2, 20	
4	9999		
23	5.15		7.94
25	2.06		5.64
27			10.68
28			0.8
29	1.44		1.21
30	5.49		2.32
33	9999		6.1
40			5.52

Cpd	LIGASE E3 APC2/APC11 H E1	LIGASE E3 APC2/APC11 H E1/GEL	LIGASE_E3 MDM2/P53
45			9999
46	0.91		4.92
50	3.7		2.69
51	12.1		9.24
54	0.035		0.074
55	0.15, 2.5, 5	4, 10	
63	0.2		
65	9999		100
69			14.24
75			13.63

Cpd	LIGASE E3 APC2/APC11 H E1	LIGASE E3 APC2/APC11 H E1/GEL	LIGASE_E3 MDM2/P53
77			0.81
82	5		1.5
96	10		0.56
98			11.59
99			0.21
103	0.3, 0.5	0.6, 2	3.87
116	5		
145	10		
146	10		
148	0.3, 0.4	1, 2	
153	3, 20	2	
160	1	0.6	
172	2	2	
174	20		
175	1.5	1, 2	
176	0.4. 0.7	0.6, 10	
177	0.4	2, 20	
183	0.1		

Cpd	LIGASE E3 APC2/APC11 H E1	LIGASE E3 APC2/APC11 H E1/GEL	LIGASE_E3 MDM2/P53
199	0.1		
238	5		
244	9999		
254			24.84
256			0.53
269	20		
270	3	9999	
271	20		
272			
274	0.11		1.18
275	0.32		1.16
278			5.21
280	0.56		0.25
299	9999		0.45
301	0.41		0.93
302			4.6
305			10.82

Assay Example 3

ROC1/CUL1 Ubiquitin Ligase Assay

[0083] Inhibition of ubiquitin ligase activityof E1+E2+E3 was measured using the protocol as described in WO 01/75145 with E3 as the ROC1/CUL1, ROC1/CUL2, or ROC2/CUL5 complex.

Materials and Methods

[0084] The wells of nickel-substrate 96-well plates (Pierce Chemical) are blocked with 100 µl of 1 casein/phosphate buffered saline (PBS) for 1 hour at room temperature, then washed with 200 µl of PBST (0. 1% Tween-20 in PBS) 3 times. To each well is added the following Flag-ubiquitin (see above) reaction solution: 62.5mM Tris pH 7.5, 6.25 mm $MgCl_2$, 0.75 mM DTT, 2.5 mM ATP, 2.5 mM NaF1, 2.5 nM Okadaic acid, 100 ng Flag-ubiquitin (made as described above).

[0085] The buffer solution is brought to a final volume of80 µl with Milipore-filtered water, followed by the addition of 10 µl DMSO.

[0086] To the above solution is then added 10 µl of ubiquitination enzymes in 20 mM Tris buffer, pH 7.5, and 5% glycerol. E2-Ubch5c and E3-His ROC1/Cul1, ROC1/CUL2, and ROC2/CUL5 are made as described in WO 01/75145. E1 is obtained commercially (Affiniti Research Products, Exeter, U. K.). The following amounts of each enzyme are used for these assays: 5 ng/well of El; 25

nl/well E2; and 100 ng/well His-E3. Varying amounts of compounds according to the invention are added and the reaction allowed to proceed at room temperature for 1 hour.

[0087] Following the ubiquitination reaction, the wells are washed with 200 µl of PBST 3 times. For measurement of the enzyme-bound ubiquitin, 100 gel of Mouse anti-Flag (1:10,000) and anti-Mouse Ig-HRP (1:15, 000) in PBST are added to each well and allowed to incubate at room temperature for 1 hour. The wells are then washed with 200 µl of PBST 3 times, followed by the addition of 100 µl of luminol substrate (1/5 dilution). Luminescence for each well is then measured using a fluorimeter.

[0088] Compound 284 was found to have a ROC1/CUL1 IC_{50} of 800 nM, a ROC1/CUL2 IC_{50} of 800 nM, and a ROC2/CUL5 IC_{50} of 200 nM. Compound 304 was found to have a ROC1/CUL1 IC_{50} of 1 µM, a ROC1/CUL2 IC_{50} of 1 µM, and a ROC2/CUL5 IC_{50} of 800 nM.